

Food and Drug
Administration Center
for Veterinary Medicine

“General Public Meeting”

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FOOD AND DRUG ADMINISTRATION
CENTER FOR VETERINARY MEDICINE

GENERAL PUBLIC MEETING

Welcome and Introduction

by Dr. Stephen Sundlof,

Director, Center for Veterinary Medicine

(1:15 p.m.)

DR. SUNDLOF: I think we're all hooked up here and ready to go. Good afternoon, everybody. I want to welcome everybody to this community that for us is very important. We're really glad to see that there is a lot of interest out there, because we're talking about the future today and we need all the best input that we can get. If we can get the slides going --.

Before I get started, let me introduce you to some of the people that were responsible for making this happen today. I am Steve Sundlof. I am the Center Director of CVM. We have Dr. Sharon Thompson who has taken on the responsibility for coordinating our activities in the area of antimicrobial resistance. To her left is Jim Heslin. Jim is going to serve as our facilitator to make sure that we have a productive discussion this afternoon, because we have a lot of information that we need to get out and on the table within a very short period of time. Also Jon Scheid who has been responsible for putting together some of the slide presentations. We will be working to try and capture some of the thoughts that surface here this afternoon.

1 Also assisting him is Joann Kla, and finally, Aleta Sindelar who
2 has been one of the people that's been instrumental in making
3 sure this whole thing would come off. We want to thank them, and
4 again, welcome to everybody.

5 I understand that there are some people who were
6 intending to be at this meeting and didn't make it because of
7 weather. So what we intend to do is provide as much of the
8 information here today that we discuss to anybody who is
9 interested and allow them to comment to the docket.

10 (Slide)

11 DR. SUNDLOF: Okay. The objectives of this meeting
12 then are to gather comments about the next meetings. There's two
13 meetings that we are going to have in the future, the risk
14 assessment and thresholds. Well, risk assessment and threshold
15 will be covered in the meeting on December 9th and 10th, and we
16 want to make sure that we surface what are the appropriate issues
17 to discuss at this meeting, who the experts are that will need to
18 be included in the meeting so that we get the best possible
19 advice.

20 The agenda. We would like your advice in helping us
21 set the agenda for this meeting, and all of the comments from
22 this meeting will be included in the docket, which is that docket
23 number there (indicating) if you would like to write that down.
24 Any comments that you think of after this meeting can be
25 submitted to the docket.

1 There is another meeting that will be held in February,
2 February 22nd and 23rd. That will be looking at the issue of
3 pre-approval studies. So there's actually two meetings. The
4 most immediate one is going to be the one on thresholds, and in
5 there will be a risk assessment.

6 Let me just say that the bottom bullet there says we
7 are not trying to -- the purpose of this meeting is not to reach
8 consensus; the purpose of the meeting is to get people's
9 comments. This is a nondecisional meeting. This meeting is for
10 information gathering. So please keep that in mind. Legally we
11 cannot have a meeting at this time that would try and develop
12 consensus. So this is under the Federal Advisory Committee Act.
13 This is how we have to be structured.

14 (Slide)

15 DR. SUNDLOF: Regulatory course. A little background
16 in history on this. The issue of antimicrobial resistance has
17 not been a subject that lends itself easily to regulation and the
18 regulatory process. It is a very complicated subject. It is
19 virtually impossible to predict ahead of time. FDA in the past,
20 although we have struggled with this issue quite a bit, have not
21 really proposed a regulatory scheme for dealing with the issue of
22 antimicrobial resistance for the reasons I have just mentioned,
23 scientific complexity, the fact that there is a lot of
24 information that we just don't have that would be extremely
25 useful in developing a regulatory approach to this, but we ,

1 decided that now is the time to move forward on this despite all
2 of the obstacles. We think this is important, because as I
3 indicated, there has been lack of information. We are starting
4 to see more information now, some good scientific studies out
5 there that definitely point to an association between the use of
6 antimicrobials in animals and certain foodborne infections in
7 people. So based on the mounting evidence, we think it is time
8 to try and move forward. We also recognize that there certainly
9 is a need for antimicrobial drugs in animals, and we somehow have
10 to strike the appropriate balance between our responsibilities to
11 public health while making sure that there is a rational avenue
12 that will allow these drugs to be used under whatever conditions
13 are appropriate in food animals.

14 (Slide)

15 DR. SUNDLOF: We declared publicly last November that
16 we believe the time has come for the FDA to take a different
17 approach to really start concentrating on the issue of
18 antimicrobial resistance in the regulation of animal drugs. That
19 appeared in *The Federal Register* last November, and it is also on
20 our web page. So anybody who wants to find that particular
21 document --. Basically, it said that for all uses of all
22 antimicrobials, not just subtherapeutic use, but therapeutic uses
23 as well, but we needed some additional information. We needed
24 information on resistance and also increased pathogen load that
25 sometimes occurs following the administration of antibiotic.

1 (Slide)

2 DR. SUNDLOF: In December of last year, we subsequently
3 issued a Framework Document. Now the Framework Document, it's
4 got a big long name and I can't even recall it, so we just call
5 it the Framework Document. It basically lays out the Center's
6 thinking about -- not only Center but the Agency. We did discuss
7 this within the FDA and other Centers within the FDA, and it
8 basically said look, when we got all of our best people together
9 that had knowledge on this issue, this is the kind of regulatory
10 approach we thought made the most sense, and we would like to let
11 the rest of the world now look at that and comment on it and tell
12 us where we got it right, where we got it wrong, things that we
13 need to change. It was a document that was meant to just give
14 the public our best opinion at the time as to what we thought was
15 a rational regulatory approach.

16 Subsequent to that announcement, we had a Veterinarian
17 Medicine Advisory Committee that met in January of last year who
18 further discussed this. We got a lot more discussion going at
19 that point, but it was truly meant to be a discussion piece. We
20 indicated that we wanted a lot of comments on that and that we
21 would revise our approach based on the comments. I can tell you
22 that we will have before the December meeting, we should have
23 those comments available and published. Some of them are up on
24 the home page right now.

25 (Slide)

1 DR. SUNDLOF: But the Framework concepts basically
2 looked at what is the public health risk. It is a risk-based
3 approach to dealing with the regulation of antimicrobials in food
4 animals. We introduced a concept of resistance and monitoring
5 thresholds that I'll talk about in a few seconds, and we
6 introduced the concept of having some pre-approval studies that
7 would give us some predictive value about what might happen once
8 the antimicrobial is actually out there and in use, what is the
9 likelihood that resistance will develop, how fast, and in which
10 particular organism.

11 (Slide)

12 DR. SUNDLOF: We indicated that we were trying to use a
13 risk-based approach in dealing with this subject. If you use
14 risk analysis terminology, one of the things you have to do is
15 you have to characterize the risk. The risk characterization is
16 the product of the hazard times the exposure, and so you have to
17 define both hazard and exposure.

18 Hazard in this case would be the impact on public
19 health should that drug no longer be useful because of the
20 development of resistance. That is the harm part. That is the
21 hazard part. So it is based on the importance of the
22 antimicrobial in human medicine. Not all antimicrobials are
23 equally important, and we want to identify those that are most
24 critical need. Then we wanted to look at the human exposure that
25 might be, that we would expect to occur from the use of these

1 drugs in animals and what -- how likely would humans be exposed
2 to pathogenic microorganisms that were resistant to these drugs
3 as a result of the use in animals, what exposure would be expect.

4 Then we said that based on these concepts, we would set
5 some pre-approval and post-approval requirements based on how
6 these fell out. So if you had a large hazard with a high
7 exposure, obviously the regulatory requirements would be greater
8 than for those drugs for which there is low exposure, low
9 potential exposure that may not be as important in human
10 medicine.

11 (Slide)

12 DR. SUNDLOF: Then we talked a little bit in the
13 Framework about risk management. This is really what we are
14 going to be talking about for the December 9th and 10th meeting,
15 setting resistance and monitoring thresholds. These are risk
16 management in that they lay out ahead of the approval process at
17 what point we would consider the drug to no longer be safe. So
18 the resistance threshold is that point at which it would trigger
19 some regulatory action.

20 The monitoring threshold is some earlier warning along
21 the line before you get to resistance, to the development of
22 resistance. It would mark those places where we would want to
23 take additional actions, but not necessarily withdrawing the
24 product, for instance. Those would be where we would intervene,
25 such things as further studies to determine what particular

1 practices might be driving the development of resistance, may
2 require some changes in the --- another thing.

3 (Slide)

4 DR. SUNDLOF: In addition, depending upon the drug's
5 category, where it falls out on this matrix, we may require pre-
6 approval studies. That will be the subject of the meeting in
7 February. We may require some additional post-approval
8 monitoring, other than the NARMS monitoring. That, again, needs
9 to be worked out.

10 (Slide)

11 DR. SUNDLOF: So, in comments so far we have heard very
12 loudly that there needs to be a lot of stakeholder involvement on
13 this issue. I think everybody --- has said that they want to be
14 involved in it. The decisions are risk-based, based clearly in
15 science, that there is definitely a need to clarify the
16 categorization of drugs. Everybody I think has been very
17 supportive of the National Antimicrobial Resistance Monitoring
18 System, and that that program in particular should be supported
19 to give us the greatest surveillance tool that we can put
20 together. As I indicated, we will be publishing these comments
21 before the December 9th and 10th meeting, so everybody should
22 have a chance to read through the comments.

23 (Slide)

24 DR. SUNDLOF: Again, I want to thank you all for
25 attending. I am going to ask Dr. Thompson now to come up now and

1 present some comments, and then we will go into an open session
2 where we will beseech your input. Then I will try to make some
3 feeble attempt at summarizing the comments at the end of the day,
4 and then we and adjourn by 5:00 o'clock. So again, thank you for
5 coming.

6 **Overview of Plans for the Workshops**
7 **on Risk Assessment/Thresholds and Pre-approval Studies**

8 **Presentation by Dr. Sharon Thompson**

9 DR. THOMPSON: Good afternoon. I am going to try to
10 give you a little bit of an overview of our plans for both of the
11 upcoming scientific meetings with the hope that this will really
12 allow you to give us your feedback, give more targeted feedback
13 to us. Certainly, as Dr. Sundlof indicated, I understood some
14 people were delayed or would not be able to come today, so I will
15 try to make copies of my slides available on our home page so
16 people can see those, and they may be able to send us comments
17 afterwards to the docket targeted to some of the points we have
18 highlighted here.

19 (Slide)

20 DR. THOMPSON: So as Dr. Sundlof mentioned, we
21 basically are planning two meetings. The first meeting will be
22 held the 9th and 10th of December and will focus on risk
23 assessment and the establishment of thresholds. The second
24 meeting will be held on February 22nd and 23rd of next year and
25 will look at pre-approval studies.

1 (Slide)

2 DR. THOMPSON: In general, just to make some comments
3 about our plans for the meetings, both of the meetings are
4 scheduled to be held here in the DoubleTree. They are scheduled
5 to go for the full day from 9:00 to 5:00. We are currently
6 planning to structure the meeting with both plenary and breakout
7 sessions, where we would have a plenary with everyone in
8 attendance and then divide into as much as three groups, three
9 breakout sessions to look at specific scientific issues.
10 Certainly I would like to invite you all to consider this,
11 whether this is an appropriate way to address these meeting
12 topics or whether it would be better to hold these meetings in
13 one continuous plenary session, but this at least is what we have
14 planned to this point in time.

15 The purpose of the meetings is to seek input from
16 experts on the approaches that CVM will outline at the meeting,
17 and then also to ask for suggestions on alternative approaches,
18 maybe things that we haven't thought of to this point in time.

19 As we get closer to the meeting dates, we do plan to
20 make more information, meeting agendas, potential discussion
21 documents, the risk assessment which I will discuss in a minute,
22 will all be made available through our home page. So I suggest
23 that you do consult that regularly.

24 (Slide)

25 DR. THOMPSON: As Dr. Sundlof mentioned today, the.

1 purpose of the meeting is to seek input specifically on the
2 issues that we will be outlining, what are the appropriate issues
3 to be considered underneath both of the scientific workshops,
4 suggestions on experts that CVM should invite. We have provided
5 for a certain amount of experts. We do have funds available, if
6 we do have nominations for experts, to pay for those people's
7 expenses to attend the meeting.

8 Suggestion on agenda items. Are there specific topics
9 you would like to see discussed? Then the format as I mentioned,
10 in terms of the plenary and the breakout sessions, whether you
11 think that is appropriate.

12 If you have additional comments following today, as
13 Dr. Sundlof mentioned, we do have a docket that is being created
14 and you can submit comments directly to that. Especially with
15 respect to the December meeting since it is coming up so quickly,
16 the sooner you can get us your comments, that would be
17 appreciated, because that will really enable us to move forward
18 on planning that meeting.

19 (Slide)

20 DR. THOMPSON: Okay. So let me talk first about the
21 Risk Assessment and the Establishment of Thresholds Meeting. The
22 purpose of this meeting is to discuss CVM's risk assessment
23 model, specifically to evaluate the risk to human health from
24 resistant foodborne pathogens associated with the use of
25 antimicrobials in food animals, and also to discuss our current

1 thinking as to how we would use this model to help us establish
2 resistance and monitoring thresholds in food animals.

3 (Slide)

4 DR. THOMPSON: I want to make a few comments about the
5 risk assessment. I think this will be helpful to people who are
6 not familiar with what is being discussed here so that you can
7 more appropriately give us our feedback. The risk assessment is
8 basically modeling the risk of increased duration of illness due
9 to resistant *Campylobacter* infections associated with the use of
10 fluoroquinolones in chicken. The model will allow us to relate
11 the prevalence of resistance *Campylobacter* infections in humans
12 associated with the consumption of chicken to the prevalence of
13 resistance *Campylobacter* in chickens. I will come back to this,
14 because this is really key when we talk about the establishment
15 of thresholds, the ability to make this connection.

16 (Slide)

17 DR. THOMPSON: I have had many people ask me why did we
18 pick this specific example, why are we looking at fluoroquinolone
19 resistance in *Campylobacter* in chickens. Basically, to model
20 something you do have to pick a specific case; you can't just
21 model in general what is the impact of resistant foodborne
22 disease.

23 (End Tape 1, Begin Tape 2)

24 DR. THOMPSON: -- specific example, and we picked
25 *Campylobacter* specifically because one -- it's not listed on the

1 slide, it is because we felt that there would be data available
2 to analyze this situation, and since there were a number of
3 ongoing studies, case control studies looking into this issue, it
4 really would provide the data to help us to model this that we
5 felt would be successfully.

6 In addition, we felt that *Campylobacter* is a very large
7 foodborne illness problem, and so it was an appropriate thing to
8 start with. In chicken, if you look at *Campylobacter* in terms of
9 the source of *Campylobacter*, chicken in the largest source, and
10 then certainly, fluoroquinolone is a -- fluoroquinolones are an
11 important drug in human medicine. It is a sensitive issue, so we
12 also felt that this was a good reason to start with this
13 particular example.

14 Then in terms of the direct versus indirect transfer of
15 resistance, a direct transfer of resistance is certainly easier
16 to attack, and we felt that that was more appropriate to model
17 first, although we are, and I will mention later, looking at the
18 indirect transfer issues as well.

19 (Slide)

20 DR. THOMPSON: So the problem that we are facing or we
21 are examining in this risk assessment is that basically
22 poultry -- we see that poultry get a disease, they get
23 colibacillosis, and then we are looking at treating most of those
24 sick animals with a fluoroquinolone, and as a result, there is a
25 potential for a fluoroquinolone resistance *Campylobacter* to

1 proliferate in the poultry gut. Humans can then be infected by
2 fluoroquinolone resistance pathogen by consumption of poultry.
3 Then in the scenario that we are examining here, infected people
4 may not respond to a fluoroquinolone if administered when they go
5 into the hospital or physician to be treated.

6 (Slide)

7 DR. THOMPSON: So we can estimate the current level of
8 *Campylobacter* in broilers. We can also estimate the number of
9 people who become ill from these pathogens. We can therefore
10 estimate the relationship between the level of *Campylobacter* in
11 chickens and the number of people who become ill from these
12 pathogens.

13 The data for really the whole risk assessment comes
14 from several different national surveys. I have mentioned some
15 of the information here, NARMS, CDC case control studies, and
16 Food Mat, although we are also looking at some published
17 literature studies as well.

18 (Slide)

19 DR. THOMPSON: We can also relate the incidence of
20 *Campylobacter* resistance infection in humans to the resistance
21 pathogen prevalence in poultry. This is really key when we look
22 at the establishment of thresholds. The risk assessment also
23 looks at the human cases that sought care, were prescribed
24 fluoroquinolones and were resistant to the fluoroquinolone. The
25 risk assessment model is set up to assess the human health impact

1 of infection being resistant versus susceptible, and that's what
2 we are really looking at in terms of potential harm.

3 (Slide)

4 DR. THOMPSON: So in the establishment of thresholds,
5 CVM must really determine at what level is any identified human
6 health impact unacceptable. We can look at this. The model is
7 set up to look at days of illness, days of enteric illness. We
8 can also look at it from the perspective of probability of harm,
9 what is the probability that somebody would be affected by a
10 resistant pathogen.

11 Once we determine what is acceptable in terms of human
12 health impact, and we have to look at this really in the context
13 of the Reasonable Certainty of No Harm Standard, once we
14 determine that, what is the unacceptable human health impact, the
15 model will allow us to relate that back to a resistance
16 prevalence in chickens. So we can say, okay, above a certain
17 level of resistance in chickens, that is an unacceptable -- we
18 would see an unacceptable human health impact. That would allow
19 us to determine a resistance threshold in chickens.

20 We can also use this to establish a monitoring
21 threshold. That would basically be a more conservative level.
22 It would be an early warning system to allow us to monitor that
23 and take action, mitigation action, when that level is being
24 approached.

25 (Slide)

1 DR. THOMPSON: Basically, I started out by saying that
2 the model was set up to look at a specific example, the
3 *Campylobacter* chickens and fluoroquinolones, but it is designed
4 to be able to be extrapolated to other antimicrobial foodborne
5 pathogen combinations, with additional data. It is important to
6 note, however, that there may be certain antimicrobial pathogen
7 combinations for which data are lacking. In these cases, CVM
8 must make certain assumptions to establish a threshold that
9 conservatively will protect public health. So this is certainly
10 an area where additional data would help us to be potentially
11 less conservative in any number that we would set.

12 Our current plan is to release the risk assessment in
13 advance of the December meeting. I mean it will be released.
14 Our intention is to publish that on our web page. We may also
15 publish it in *The Federal Register*. At least we will put a
16 notice out in *The Federal Register* saying that it is available.

17 I started out by saying we picked a direct foodborne
18 pathogen resistance issue to model because the indirect was more
19 difficult, but we are beginning to look at that issue as well.
20 We will be getting a risk assessment on that. That will not be
21 discussed, though, at the December meeting.

22 (Slide)

23 DR. THOMPSON: Okay. So in terms of the December
24 workshop, what are some issues that we are looking at? I
25 basically tried to write down some different issues that I

1 thought might be appropriate, specifically to be the subject of
2 breakout sessions. I am going to run through these relatively
3 quickly, and I would certainly welcome your comment on any of
4 these ideas that are being proposed or certainly to give us other
5 ideas as well.

6 One area would be to discuss the model itself, what are
7 comments on the limitations of the model, identification of any
8 significant data gaps in the model, comments on positive aspects
9 of the model and also certainly aspects that you recommend that
10 need to be changed, and then how can we use the model to help the
11 industry reduce the risk, the level of risk that is identified.

12 Another area of interest, because this is relatively an
13 innovative approach to modeling this issue, so a thought would be
14 to have a session on mathematics, the mathematics of the model.

15 Use of the model for other antimicrobial foodborne
16 pathogen combinations, how would we do that, what would be the
17 assumptions we would potentially need to look at to allow us to
18 make that extrapolation.

19 (Slide)

20 DR. THOMPSON: I highlighted the mechanisms we plan to
21 use this to establish thresholds, how would we do this, how
22 should this relate to the Reasonable Certainty of No Harm
23 Standard. When we do put the model out, we will discuss this in
24 the risk assessment, but certainly we would be looking for
25 feedback on that; is that an appropriate standard to use, for

1 instance, are there other appropriate standards, have we chosen
2 the right level.

3 Then, how should we view the population of concern?
4 Depending on how you define the population of concern, it will
5 have a big impact on the level of risk that is identified. So
6 should we look at it from the perspective of the entire U.S.
7 population, those individuals with *Campylobacter*, or more
8 specifically or narrowly those seeking care and requiring
9 treatment for resistant pathogens? So obviously that is the
10 smallest population of all.

11 Then how can industry assist the Agency in obtaining
12 data to reduce the uncertainty in the model? We will highlight
13 that, the areas of the model where we really could use additional
14 data, where we are most confident about the data that is there
15 and where we are the least confident.

16 Then potentially another session could be on
17 appropriate mitigation actions to be taken when monitoring
18 thresholds are reached.

19 So just to go back to the start, we really are seeking
20 input on the appropriate issues. Are some of these that I have
21 highlighted, are these the right issues, are there others that
22 should be included? Suggestions on experts who really can give
23 us input, scientific input on these areas. Suggestions on
24 additional agenda topics. The format, is breakout sessions a
25 good approach?

1 (Slide)

2 DR. THOMPSON: I am going to move to the workshop on
3 pre-approval studies. In this you will see there is a lot less
4 thought at this point in time on this workshop, and that is
5 because we have a little bit longer to plan for it. But the plan
6 of this workshop is to discuss our thinking on the appropriate
7 design of pre-approval studies in food animals to model the rate
8 and extent of resistance development.

9 (Slide)

10 DR. THOMPSON: We are really looking at three basic
11 areas of concern. We are looking at the potential transfer of
12 resistance foodborne pathogens to humans, the transfer of
13 resistant determinants from a foodborne bacteria to a pathogen
14 within the human GI tract, and then also pathogen load, increase
15 in pathogen load in the target animal as a result of treatment
16 with a new animal drug, and basically looking at not only the
17 increase in the total population of shed pathogens, but also
18 looking at the fractions in terms of the population of pathogen
19 shed.

20 (Slide)

21 DR. THOMPSON: CVM basically is approaching these
22 concerns at this point in time with the design of pre-approval
23 studies. The pre-approval studies would be used to predict the
24 time it would take under actual use conditions to see changes in
25 susceptibility to the drug, and the studies would also look at

1 the magnitude of the changes in susceptibility to the drug. The
2 final area is looking at pathogen load, determining the potential
3 of the drug to increase pathogen load in the target animal.

4 (Slide)

5 DR. THOMPSON: In addition to the general questions on
6 issues, format, agenda and experts, with respect to the Pre-
7 Approval Studies Workshop, we would really like to ask for
8 comment on whether or not we should plan to hold two separate
9 workshops, one to look at resistance and one to look at pathogen
10 load, or whether both of these topics should be dealt with in the
11 February meeting.

12 The pros of looking at both topics is obviously we
13 would open the discussion on both early. So that is a definite
14 advantage. There is some thought that that may also facilitate
15 the design of study protocols to address both of these topics in
16 one study rather than two separate studies. So we feel that that
17 is an advantage.

18 Our concern, however, is that trying to deal with both
19 of these topics in only two days we may end up giving short
20 shrift to the topics, that we really wouldn't come up with any
21 recommendations at the end of the meeting. Also, as a result of
22 that, we may actually delay our overall guidance with respect to
23 these areas because we have not dealt with either of the topics
24 adequately in this one meeting. So I would certainly like to
25 hear some feedback on this, whether people think we should deal

1 with this in one meeting or two meetings, and that will help us
2 make a decision as to how we move forward.

3 So I am going to stop there, and I apologize for taking
4 a little bit longer than I had initially planned on the agenda,
5 but I did feel it would be helpful to go over the risk assessment
6 and give you some sense of what that is going to do and how we
7 would use that to establish thresholds. So I am going to finish
8 my remarks and we are going to go ahead and open up -- I am going
9 to turn it over to Jim Heslin to help us manage the public
10 commentary. Thank you.

11 Public Comments on Risk Assessment and
12 the Establishment of Resistance Thresholds
13 and Pre-Approval Studies Workshops
14 Moderated by Mr. Jim Heslin

15 MR. HESLIN: Good afternoon. In just a minute I will
16 invite you forward to make your comments, but there are a couple
17 things I wanted to go over first. Just to restate that the
18 purpose here is to get comments and input on these two, on the
19 design and development of two scientific workshops. To that end,
20 we are looking for the scope, the format of the workshop,
21 comments on the issues, the possibility of experts that could be
22 involved in this process. So there is really a broad area here
23 that is open for you to comment on, and this is an opportunity
24 for you to let the Center for Veterinary Medicine hear your
25 thoughts on how these workshops should be designed. Dr. Sundlof

1 and Dr. Thompson may ask questions for clarity, but primarily
2 their role is to listen to your comments and suggestions.

3 There are three microphones across the front of the
4 room. You can use whatever one you choose. Be careful. I think
5 the cords are pretty well taped down, but just watch yourself as
6 you go to the microphone.

7 If you have additional comments to submit, for those of
8 you who have picked up the handout "CVM Update," listed in there
9 is the docket number and the address to send any written comments
10 to.

11 In order to get a better sense of how much time we can
12 allot both for the first part of the discussion which has to do
13 with the risk assessment and establishment of resistance
14 threshold workshop, that is one piece. Then we are going to take
15 a break and then come back to pre-approval studies in
16 antimicrobial resistance. So try to limit your comments to the
17 appropriate workshop in each phase here. Regarding the first
18 workshop, how many individuals or organizations intend to make
19 comments?

20 (Show of hands)

21 MR. HESLIN: Okay. All right. Well, I think we were
22 going to try to limit this to five minutes for your comments. I
23 will give you a heads-up when you have about a minute left so you
24 can close that out. I would ask that when you come forward you
25 identify yourself and your organization. Okay. Any questions

1 about the process?

2 (No audible response)

3 MR. HESLIN: Okay. Who is first? I did see some hands
4 raised. Yes.

5 DR. CARNEVALE: Thank you. I am Dr. Richard Carnevale.
6 I am Vice President for Scientific, Regulatory and International
7 Affairs for the Animal Health Institute. AHI represents
8 manufacturers of pharmaceuticals, feed additives and biological
9 products for use by the animal community.

10 On behalf of the Institute and its member companies, we
11 appreciate the opportunity to appear before you today to provide
12 our views on CVM's upcoming workshops on risk assessment and the
13 establishment of resistant thresholds and pre-approval studies
14 for antimicrobial resistance.

15 In addition to our comments today, I also have prepared
16 remarks which I would like to submit for the record.

17 (Document Submitted, See Appendix)

18 DR. CARNEVALE: We will also provide comments later as
19 to our recommendations for experts that might be applicable to
20 each of the various components of the planned workshop.

21 AHI recommends a workshop format that provides
22 participants with a briefing on the critical issues impacting and
23 influencing the topics under discussion followed by breakout
24 sessions to examine simultaneously multiple topics by appropriate
25 experts, and a closing session for bringing together the various

1 elements.

2 Additionally, we would encourage CVM to begin each
3 workshop with a clear statement of the purpose of the workshop,
4 what they envision as the end product of the workshop, and what
5 next steps will be after the conclusion of the program.

6 AHI believes a general discussion of the application of
7 and differences between risk assessment and risk management would
8 be an important introductory session to be addressed in the
9 plenary. Another key topic for the plenary is the area of
10 microbiological breakpoints and how they are usually determined
11 and used by the medical community.

12 AHI recommends, further, the following topics for
13 discussion by experts and workshop participants during the
14 breakouts, and I might add that a number of these recommendations
15 tie very closely with ones Dr. Thompson has already recommended:
16 first, an analysis of the components of the CVM Risk Assessment
17 Model and how probability estimates have been applied to the
18 populations at risk; a discussion of the use of in vitro
19 sensitivity data, susceptibility data, and breakpoints as
20 reliable indicators for predicting human health impact; an
21 examination of how to define both a monitoring and a resistance
22 threshold and how they would be evaluated and enforced; a
23 discussion of the possible mitigation steps if a threshold is
24 reached; since a risk assessment is a dynamic process, a
25 discussion of how ongoing changes could be evaluated and

1 incorporated into the risk assessment model, including how the
2 model might be applied to existing products; and finally, a
3 review including both policy and legal issues of the application
4 of the standard "Reasonable Certainty of No Harm." We believe
5 this is a critical discussion, since this standard is the
6 foundation for setting thresholds. We believe there are valid
7 questions as to whether the standard, as applied to the approval
8 process, is properly applicable to actions the FDA may take in
9 attempting to control antimicrobial resistance.

10 As I said, we will submit formal comments for the
11 record, and we will follow it up later this week with
12 recommendation on experts. Thank you for your time.

13 MR. HESLIN: Thank you. Any questions of clarity?

14 (No audible response)

15 MR. HESLIN: Okay. Yes.

16 MR. WOOD: I am Richard Wood, Director of Food Animal
17 Concerns Trust. We do not have formal comments to present today,
18 but I have some informal comments that I would like to make in
19 reference to what has just been presented here and to the
20 materials and perspectives that were offered in *The Federal*
21 *Register*.

22 We have been very concerned, as others have been I am
23 sure, about what the status is on the implementation of this
24 Framework Document. I remember when it was first presented and
25 then at the first public meeting on this last January, it was our

1 impression that implementation of this document would happen in a
2 very timely fashion, and even April was talked about as a target
3 date for a following guidance document on this question. We
4 support that continued sense of urgency. We are dealing with
5 situations that do threaten public health, and any further delay
6 really puts that public health at risk. So we would hope that,
7 and I came to this meeting with a deep concern that the steps
8 would be steps that were scientific steps, yes, but also perhaps
9 steps that would further express the science of delay, and that
10 really cannot happen. What Dr. Thompson laid out here I think
11 was a procedure that might move us forward and might hasten the
12 time when we actually do see a Framework implemented, and I
13 appreciate that description that you provided us, and that would
14 lead the comments particularly dealing with pathogen loads ---
15 given the next section.

16 But also because of the delay and our concern as a
17 consumer organization and a group also that focuses on on-farm
18 management strategies, we are deeply concerned that any next
19 steps be laid out have a high degree of public accountability
20 laid into -- built into them, so that questions be addressed as
21 to who's in charge of this process, who are the key actors that
22 we can turn to who are making the decisions, what are the
23 deadlines that we can expect that will be met, when will we see
24 the questions that we identify at these ensuing workshops
25 answered, and when will we have a report back in terms of the

1 results of these studies.

2 I really appreciated hearing that we are going to
3 finally see the comments that many of this in this room submitted
4 months ago, and we have been wondering when we were going to see
5 those comments so that we could view how others were responding
6 to this issue. So that becomes a very important part of the
7 whole public accountability. I am concerned --

8 MR. HESLIN: ---

9 MR. WOOD: I see --- giving me a minute.

10 MR. HESLIN: The accountability piece, is that part of
11 the workshop? Are you proposing that as part of the workshop?

12 MR. WOOD: I think, yes. I think at the workshop, I
13 think that items -- a part of the workshop ought to identify what
14 kind of accountability we would like to see from CVM in terms of
15 what we expect to be fulfilled and what should be publicly out
16 there in front of us in terms of shared deadlines. I mean, we
17 shouldn't be setting the deadlines, but I want to know what the
18 framework is for the deadlines. I want to know, I think we ought
19 to know, you know, when are we going to know who is making those
20 decisions and when those decisions will be published and a part
21 of the public record.

22 I am concerned, and this is -- I am not a scientist, as
23 I am sure you recognize, but I am concerned about the risk
24 assessment. On one hand, I am heartened by the risk assessment
25 focusing on fluoroquinolones in relationship to *Campylobacter*

1 resistant bacteria because studies are showing that this is a
2 high risk area, but we're looking at here a Category I drug, if
3 we were to impose the Framework Document. For a group such as
4 ours, Category I drugs, we're really even questioning whether
5 there should be a Category I in the Framework Document. By using
6 fluoroquinolones as the example par excellence, is there some
7 implicit approval of its use and providing mechanisms to see how
8 it might be used in an efficacious way, when in fact some basic
9 questions as to whether or not that question should be on the
10 table in and of itself should be addressed? So a part of the
11 workshop might be to look at the very nature and substance of the
12 risk assessment model itself in terms of the drug choice and its
13 focus for our own debate.

14 We have participated in -- finally, in terms of the
15 risk assessment, we would hope that the question of what data is
16 needed would be clearly discussed. We agreed with the parts of
17 the Framework Document that said that we do need to have drug
18 sale and use data, and we would hope that in this risk assessment
19 that is being completed that drug use and sale data would be a
20 part of that fluoroquinolone study as well.

21 MR. HESLIN: You have about a minute left.

22 MR. WOOD: Okay. Thank you. In terms of thresholds,
23 again, there would be questions of public accountability clearly
24 identifying who is going to be at the table when those
25 thresholds -- or what types of people, what categories, what

1 groups of people would be at the table when those threshold
2 decisions are actually made in this risk management model. We
3 would be concerned that consumer representatives are a part of
4 that and also which experts would be there. We would like to be
5 a part of the discussion of developing that list and appreciate
6 the opportunity to develop that list as others have been offered
7 that as well.

8 Regarding the format, we have been through several now
9 workshops where the FDA has been one of the leaders where we have
10 had breakout groups and round tables. We have also in the past,
11 all of us in the room I am sure have, been a part of meetings
12 where we have all sat around one big table. Certainly the small
13 breakout rooms and tables are more inclusive in terms of sharing
14 information, but at some point in these workshops, I would hope
15 that we would come to one big table where comments and debate and
16 discussion would be a part of the public record and where
17 together we could come to consensus, as opposed to having eight
18 different consensuses (sic) around eight different tables. That
19 kind of discussion is very important I think to any kind of work
20 that we come to from all of our various vantage points. Thank
21 you.

22 MR. HESLIN: Thank you. Anyone else with comments on
23 this particular workshop that is being proposed? Yes.

24 MR. DODEMAIDE: Good afternoon. My name is Robert
25 Dodemaide. I work for Hoechst Roussel VET in Clinton, New

1 Jersey, but I am speaking personally. At this forthcoming
2 workshop in December, I would dearly like to have included
3 amongst the invited experts people such as the bovine
4 practitioners, the swine practitioners, the poultry pathologists,
5 those specialist groups, because I feel that each of those groups
6 has issued its own steps in order to lessen the risk of the
7 transference of resistance factors from animals to either
8 zoonotic pathogens or to other organisms which might infect the
9 human gut. So I urge CVM to consider those specialist groups who
10 I think can have -- can give us a lot of input on steps that are
11 required to help assess the risk and to manage the risk. I think
12 with those groups at the table we will have a far better idea
13 about what's required. If those groups are absent, I think a lot
14 will be missing and we could well come to the wrong conclusions.
15 Thank you.

16 MR. HESLIN: Thank you. Yes.

17 MR. SCHILARK: I am Tom Schilark. I with the Lanco
18 Animal Health. The comments that I wish to contribute would be
19 made from the standpoint of the National Committee on Clinical
20 Laboratory Standards. This is a group of which I chair the
21 Veterinary Antimicrobial Susceptibility Testing Subcommittee.
22 This particular organization is involved with setting breakpoints
23 as well as setting the methodology and quality control for
24 conducting in vitro susceptibility testing. The organization is
25 national in scope. It has international outreach as well.

1 In addition to the veterinary side which is just
2 beginning, there is also a very long history of this sort of
3 thing with the human antibiotics. I think as we move forward it
4 would be incumbent upon the workshop to have a presentation from
5 members of the NCCLS, perhaps both from the human as well as the
6 veterinary sides of things, to lay out what is available as far
7 as methodology for laboratories, as far as breakpoints are
8 determined and how these may be used in actual clinical medicine
9 practice. There is a lot of information that is generated and a
10 lot of decisions which will be made based upon these MICs, so I
11 think as a way to start a foundation for discussion, some of
12 those sorts of things should be brought forward. Thank you.

13 MR. HESLIN: Thank you. Yes.

14 DR. LEIBERMAN: Hi. My name is Patti Leiberman from
15 the Center for Science and Public Interest, and I want to also
16 speak sort of casually today. I want to first of all reiterate
17 some of the comments that Rich Wood made from FACT that CSPI is
18 concerned about, the fact that this is a very painfully slow
19 process. We are concerned that CVM doesn't feel the same urgency
20 that is felt in the consumer groups, that it's been 10 months
21 since putting out the Framework, and this schedule calls for only
22 meetings and discussions through February. In the meantime, we
23 have the CVM approving new combination drugs that include
24 antibiotics such as virginiamycin while we have a petition
25 pending that's been submitted by CSPI and 40 other consumer and

1 health groups, and new CDC data on resistance is relevant to
2 that.

3 Now, we have some general concerns about the Framework
4 that we have made in our comments before. One has to do with the
5 categorization of the kinds of drugs. It seems difficult for us
6 to talk about how we would set thresholds for these things if we
7 don't have the categorization done ahead of time, before we
8 discuss it, because as Rich said, some of these Category I drugs
9 we feel really shouldn't even be -- I mean, there might be no
10 threshold of resistance that would be acceptable to us.

11 We have concerns about waiting for a risk assessment
12 and waiting for data when we know that the drug companies have
13 not been forthcoming in giving drug use information. Perhaps
14 they will change their tradition of not giving that information.

15 We wanted to make sure that the upcoming scientific
16 meetings really were mostly composed with people who are experts
17 in public health, microbiologists, also with some input from
18 consumer groups, but for the thresholds, that the focus needs
19 to -- especially for the meeting with thresholds, the focus of
20 the expertise should be on people who are thinking of human
21 health, with animal health obviously being a factor. We suggest
22 considering some of the experts, the scientific expertise from
23 the European community where they have made policy decisions with
24 the data that they have to try to move forward on this issue.
25 Thanks very much.

1 MR. HESLIN: Thank you. Anyone else with comments on
2 this particular workshop? Yes.

3 DR. SHELDON: How do you do. My name is Al Sheldon. I
4 am a team leader in the Division of Antiinfective Drug Products.
5 We are responsible for the review of antibiotic new drug
6 applications with -- that are used in humans. I would like to
7 reiterate the last point that was made about using experts from
8 the scientific community in Europe who have done a lot of work to
9 try to identify some of the risk factors associated with use of
10 antibiotics, not only in animals but also in human medicine, and
11 to invite individuals from the human community to try to
12 understand the risk factors that have been defined there also,
13 because we are in fact not independent of each other but actually
14 occupy the same ecological niches, and we need to have an
15 understanding of how the use of antibiotics and the ecology niche
16 which we all occupy is playing a part in antibiotic resistance.

17 Secondly, I would like to note that the FDA, the
18 microbiologists in the Division where I work, are responsible for
19 the setting of interpretive criteria, that is breakpoints, that
20 are used in package inserts. I am a member of the NCCLS, and I
21 am a voting member of the AST, which is the Antibiotic
22 Susceptibility Testing group, and I would like you to invite the
23 FDA microbiologists to make a presentation on the establishment
24 of interpretive criteria from the regulatory perspective within
25 the Agency.

1 MR. HESLIN: Thank you. Anyone else for this round of
2 comments? Yes.

3 DR. ANGULO: I am Fred Angulo from the Centers for
4 Disease Control. I also would like to join those who have voiced
5 support for the Framework Document and the momentum that is
6 occurring here with the establishment of these public meetings,
7 and I think this input is critical and essential and applaudable,
8 although I also join with others saying that I think it would be
9 very useful to have a vision on the implementation dates so that
10 people could understand, at least in broad terms, when final
11 regulations -- final implementation might be in place. I know
12 that dates tend to change over time, but just a regular --
13 general thoughts on implementation would be very useful.

14 The specific comment is that I think much of the
15 discussion on the Framework Document, the extremes of the
16 discussion, could be moderated if it was clear what the
17 categorization of the drugs were. So I think that some of the
18 concerns that on one extreme people are concerned that all drugs
19 used in food animals would be categorized in a high value or a
20 low value, that once it's clear which drugs are Category I, then
21 perhaps that the movement towards implementing the Framework
22 might proceed anew. So I would encourage holding the necessary
23 meeting to categorize the drugs in the near term, and perhaps
24 even before the December meeting have a straw man categorization
25 of the drugs which would help some of the discussion at the

1 December meeting.

2 MR. HESLIN: Thank you. Yes.

3 MR. UNOWSKI: Joe Unowski. I am a reviewer in the
4 Department of Antiinfective Drugs Products working with
5 Dr. Sheldon. It's concerning the categorization of drugs.
6 Genetic resistance is most often linked genetically, and I think
7 we should have some genetic experts to discuss the problem of
8 carrying along other drug resistances besides the ones we are
9 majorly concerned with, because resistance to fluoroquinolones
10 can prolong resistance to other drugs, for example. So I would
11 like to see some genetic experts to discuss this.

12 MR. HESLIN: Thank you. Any other comments at this
13 point?

14 (No audible response)

15 MR. HESLIN: Okay. If I could get a show of hands as
16 to the number of people who want to make comments for the Pre-
17 Approval Studies Workshop.

18 (Show of hands)

19 MR. HESLIN: It looks like just one.

20 (Show of hands)

21 MR. HESLIN: Just a couple folks. Should we take a
22 break and come back to that, or just continue on?

23 (Brief recess)

24 MR. HESLIN: Yes. I think there were two that raised
25 their hand. Okay. I think after the comments Dr. Sundlof and

1 Dr. Thompson will need a few minutes to get their thoughts
2 together on the summary of the discussion and the next steps, so
3 at that point we can take a quick break.

4 Okay. Shifting gears to the Pre-Approval Studies in
5 Antimicrobial Resistance Workshop. Did someone here raise their
6 hand? Yes. If you could reintroduce yourself.

7 DR. CARNEVALE: Yes. I am Dr. Rich Carnevale again
8 with the AHI. Our comments on pre-approval will be very brief
9 because we haven't really had a chance to think about that as
10 much as we have had the threshold workshop. On the question with
11 regard to whether there needs to be a separate workshop on
12 pathogen load, I don't have a formal opinion on that at the
13 moment. It may have some merit to have a separate workshop. We
14 will have to go back and think about that, to that specific
15 question that Dr. Thompson posed.

16 A couple of thoughts, though. We do think that a
17 workshop on pre-approval needs to right at the beginning state
18 the real purpose for the pre-approval studies and exactly what
19 value the pre-approval studies have and how they will be used in
20 the evaluation process. We think that is very important, because
21 I know AHI in looking at this Framework Document has been a bit
22 confused at times of how all the pieces fit together and what
23 value all the pieces have in the process of evaluating
24 antimicrobial resistance.

25 A couple of specific points we would make that needs to

1 be included in the workshop, we believe, is there have been over
2 the years a requirement for microbiological studies under
3 21CFR55815 for the continuous feed additive products, as they
4 say, continuous feed additive products, longer than 14 days I
5 believe in duration. There is a lot of experience with those
6 studies, both the industry and the people that conduct those for
7 the industry, and we think a presentation by people that have
8 conducted those studies as to the value of those studies or the
9 lack of value of those studies as the case may be, and what they
10 have shown from conducting them over the last 10 to 15 years. So
11 that is a key part of I think this workshop, is to have that
12 right at the beginning.

13 Also, we think that there is a lot of data that is
14 currently collected by pharmaceutical companies, both the human
15 side of the company as well as the veterinary side of the
16 company, on microbiologic information and the microbiologic
17 qualities of the products that are being -- the compounds that
18 are being discovered and developed. We think it is very
19 important to have an expert provide an overview of how a compound
20 may be taken from discovery to final approval on the veterinary
21 side to really give the audience a comprehensive picture of what
22 really goes into a new animal drug application. We are concerned
23 at times that there may be a lot of misinformation as to exactly
24 what kind of data is collected and generated for antimicrobial
25 products that go into veterinary use.

1 We have submitted formal comments as well, back when
2 the Framework Document was first issued. There was a request for
3 formal comments, and we did provide some 60, 70 pages of comments
4 on all phases of that document. We resubmit that for your
5 convenience. In that is a section specifically aimed at pre-
6 approval studies with some suggestions for how pre-approval
7 studies, if they are going to be required, might be conducted.
8 So I submit that for your information as well, and as we get
9 closer to that workshop, I am sure we will have further and more
10 detailed comments to make as further information comes out.

11 Thanks.

12 (Documents Submitted, See Appendix)

13 MR. HESLIN: Thank you. Yes.

14 MR. WOOD: I am Richard Wood with Food Animal Concerns
15 Trust. My comments as well are very brief. We of course are not
16 the experts in the new animal drug approval process, which leads
17 to one of our first concerns, and that is that who are the
18 experts that we put together for this and what kind of review or
19 discussion might there be around that panel. We would be
20 identifying some people that has come from our reading of the
21 scientific literature, but I think that is, for us anyway, a very
22 critical question.

23 I came to this meeting not knowing what you were going
24 to be presenting, Dr. Thompson, but one of the things on my list
25 was a concern that the pathogen load was not being addressed. It

1 was good to see that that side of the equation and what happens
2 to the intestinal fluor was being put on the table. I can't
3 answer it from our perspective whether that needs to be a part of
4 one meeting or a second meeting. Again, I bring you our primary
5 concern, is that we move forward, so, whatever facilitates that
6 and causes that to happen.

7 Finally, more of a question than a comment on another
8 part of this whole Framework package that may or may not be a
9 part of either of these workshops but I think is important and
10 does need to be addressed, is the post-approval monitoring
11 process. It may be a part of this second workshop, if in fact
12 post-approval monitoring is built into the drug approval process,
13 where there are agreements made at that point, but I know there
14 has been some discussion as to where that post-approval
15 monitoring would take place. I think that discussion needs to be
16 continued. I believe the Framework Document lays out that the
17 post-approval monitoring take place perhaps on-farm. We would
18 support that, but there are a number of issues involved in doing
19 that would -- that deserve some discussion and consideration by
20 all of us in this room. Thank you.

21 MR. HESLIN: Thank you. I think there is a gentleman
22 who walked in just a couple of minutes ago. Here is your
23 opportunity to comment if you want to do so.

24 (No audible response)

25 MR. HESLIN: Okay. I think that concludes the public

1 comment piece. Let's go ahead and take a break. Twenty minutes
2 sound about right? Will that give you enough time?

3 DR. THOMPSON: Yes.

4 MR. HESLIN: Okay. If you want to, reconvene in 20
5 minutes. I believe there is coffee outside.

6 (Brief recess)

7 MR. HESLIN: Okay. If you will take your seats, we
8 will get started again. For the remainder of the time we have
9 here this afternoon, Dr. Sundlof and Dr. Thompson will be feeding
10 back to you what they heard in terms of comments and suggestions
11 on these two workshops. It is an effort to ensure clarity and
12 understanding. If there is something you want to add to
13 supplement, fine, but this is not a new discussion point. It is
14 confirming what was heard earlier.

15 Before we do that there are two things. A question
16 came up about the docket number and which docket number to submit
17 the comments on each of the workshops to. Either workshop goes
18 to the same docket number. I think there was some feeling that
19 maybe it was just for one, and they were looking for -- somebody
20 was looking for a docket number for the other one, but both
21 workshops, same docket number.

22 Also, there were some additional comments, and I want
23 to just open this up for a new minutes, that were sent in for
24 Mr. Wages to make, and so we will go ahead and do that now. Just
25 identify yourself and your organization.

1 DR. WAGES: I am Dennis Wages, and I am representing
2 the American Veterinary Medical Association. The AVMA were going
3 to withhold their comments and basically not have any public
4 comments that were going to be written. Certain aspects from the
5 bovine practitioner and avian pathologists have written some, and
6 I am just going to read them. I don't know their background, but
7 I will read them as they have been presented to me.

8 The first was, "The American Association of Bovine
9 Practitioners Committee on Pharmaceutical and Biological Issues
10 look forward to participating in the December and February
11 meetings related to antimicrobial resistance in food-producing
12 animals.

13 "We strongly feel that the existing degree of risk of
14 antimicrobial resistance in humans due to antimicrobial use in
15 animals should be determined. Without an assessment of the
16 overall risk to people of antimicrobial use in animals,
17 monitoring of effects of policies to reduce resistance in people
18 with changes in antimicrobial use or availability for animals
19 would be meaningless. A reduction in risk implies that there is
20 a value for risk.

21 "Likewise, a value for risk is necessary to determine
22 the cost of interventions intended to reduce the risk. For
23 example, if an intervention costs \$10,000 and it reduced the risk
24 from an estimated 5 work days lost per case of sickness due to
25 antimicrobial resistance caused by antimicrobial use in food

1 animals to 4.75 work days per case, policy makers would have to
2 decide if the \$40,000 per week (sic) day was a good public
3 investment." I hope you all followed that.

4 (Laughter)

5 DR. WAGES: "Similarly, thresholds should be determined
6 based on calculations intended to show that above a certain level
7 risk will change. If an antibiotic with an easily attainable MIC
8 for a selected pathogen is found to have a small shift in MIC,
9 the risk may remain constant.

10 "In summary, without a beginning assessment of the risk
11 of antimicrobial resistance in humans due to the use of
12 antimicrobials in animals, the need to establish resistance
13 thresholds, change pre-approval studies, or the effect of any
14 other policies to reduce risk would be difficult to measure.

15 "We would encourage the participation in the future
16 meetings of Drs. Kathy Ewert and Dave Dargatz. We feel that both
17 have demonstrated knowledge and impartial judgement important to
18 the success of the meetings.

19 "The American Association of Bovine Practitioners very
20 much looks forward to participating (sic) by member veterinarians
21 and other experts at the December 9th and 10th and February 22nd
22 and 23rd meetings."

23 Next fax. "Concerning workshops on risk assessment and
24 establishment of resistance thresholds, this may be the place to
25 try to get CDC and CVM to clearly articulate is there a degree of

1 risk to human health that is or would be acceptable from the use
2 of antimicrobials in animals. At some point such a threshold
3 should be established.

4 "If we are left with the answer of 'none,' they would
5 have full leeway to pursue any punitive programs that is
6 politically possible. In other words, we would hope risk
7 assessment, as it is used here, would be the assessment of
8 overall risk. We are concerned that risk assessment by their
9 definition what is really meant is a separate issue" -- excuse
10 me, "is risk of reduction, which is a separate issue and changes
11 the intention of the meeting entirely. Hopefully, Dr. Lester
12 Crawford could speak to this from Georgetown University, or
13 Dr. Harley Moon with his experience from the National Academy of
14 Sciences.

15 "If we don't establish what is the risk, calculation of
16 any meaningful cost benefit analysis, including environmental
17 ramifications of poor feed conversions, increased mortality, et
18 cetera and its effect on environment of public health, would
19 become impossible.

20 "Establishment of resistance thresholds. A key issue
21 here would be try to confine any action levels to resistance
22 development within the veterinary community rather than the human
23 community. Given the potential for resistance development within
24 the human community due to the antibiotic use there, it may be
25 inappropriate to try restriction of use of drugs in the

1 veterinary community to try to sway the resistance development in
2 the human community. Dr. Clyde Thornsburg may be a good
3 reference in this area.

4 "Pre-approval studies in antimicrobial resistance.
5 Information collected in these studies should focus bacteria
6 collected in the ready-to-eat cooked product. Collecting
7 bacteria from the farm for this purpose is not generally germane
8 to foodborne disease and tends to denigrate efforts within the
9 food processing industry to control the transmission of such
10 agents."

11 MR. HESLIN: You have about a minute left.

12 DR. WAGES: Yes, I think that's about all I got left.
13 "CVM's position might be, if they are interested in overall
14 environmental load of resistant organisms, to which the reply
15 should be, trying to prove a link between veterinarian and human
16 resistance through food supply mechanisms has been very difficult
17 in a quantitative way and that efforts to make such a
18 quantitation, they would be based on total environmental load" --
19 "being based on total environmental load, are at least premature
20 and may be in fact irrelevant." Thank you.

21 MR. HESLIN: Thank you. And with that, we will
22 transition to Dr. Sundlof who will -- I am sorry.

23 MR. : We have a clarifying --

24 MR. HESLIN: Yes. I am sorry. A question for clarity.

25 MS. : Yes. Was that a second set of

1 comments? Who was that from?

2 DR. WAGES: That was from Dr. Larry Geinder
3 Govermilling. He is a veterinarian in charge of -- I am sorry I
4 didn't say that, both poultry and swine.

5 DR. SUNDLOF: Okay. I am going to attempt to
6 summarize. In fact, I put down -- we had three different people
7 taking notes, and when we compared them we all three said
8 different things. So I strongly encourage everybody to submit
9 their comments in writing. I am going to try and summarize. The
10 only way I can see to do this is just go down through the list of
11 speakers and try and summarize what they said, and then I am
12 going to have -- and then Dr. Thompson is going to go back and
13 fill in some blanks where I missed issues. Then if the speaker
14 feels that I did not accurately capture the comments, please feel
15 free to step forward and correct the record.

16 The first presentation was by Dr. Richard Carnevale
17 from the Animal Health Institute. He talked about first of all
18 the format of the meeting and that the format should really be
19 three different parts. First of all, there should be a briefing
20 on the critical issues in plenary, including a discussion of risk
21 assessment and risk management, breakpoints and their use in
22 setting thresholds, such things as how -- well, let me go back.
23 Then have breakout sessions, and in those breakout sessions such
24 things as evaluating thresholds and how they would be enforced,
25 resistance versus loss of susceptibility, how the Reasonable

1 Certainty of No Harm Standard would be applied. Then following
2 all that would be a closing plenary session in which we try and
3 bring closure to some of the issues that were discussed and
4 propose next steps. That's what I had. Dr. Thompson.

5 DR. THOMPSON: The only thing addition that I had was
6 that -- a suggestion to also discuss ongoing changes to the model
7 and application to existing products, in terms of one of the
8 breakout sessions. That was the only other point I had.

9 DR. SUNDLOF: Dr. Carnevale, did you want to comment?

10 DR. CARNEVALE: No, I think you captured it.

11 DR. SUNDLOF: Thank you. Our next speaker was Richard
12 Wood from Food Animal Concerns Trust. He was concerned about the
13 timeliness and the speed at which we were moving forward on this
14 issue, indicating that we had originally talked about responding
15 to the comments by April and that we start responding to the
16 comments. He stressed public accountability; for instance, who
17 is in charge, who is going to be making the decision, what are
18 the deadlines.

19 Questions at workshops, when will we get some of the
20 answers that CVM has promised. There was a number of process
21 questions. He indicated that they would like to know what CVM is
22 planning, that we lay out our plan for addressing some of the
23 issues that pertain to the risk assessment and the Framework
24 Document.

25 He questioned whether the risk assessment should

1 include any risk -- any threshold for risk of a drug in
2 Category I. There was a concern that drug sale and use data,
3 which were part of the Framework Document, they are not
4 specifically mentioned anywhere and he was wondering where we are
5 on that.

6 Thresholds; who will be at the table when the decisions
7 are made, experts, consumers, et cetera. He wanted clarification
8 on who would be at the table. Dr. Thompson indicated she didn't
9 have anything else. Mr. Wood.

10 MR. WOOD: Fine. Thank you.

11 DR. SUNDLOF: Okay. Thank you. Then Robert Dodemaide
12 offered a personal opinion. He indicated that experts at the
13 meeting should include members from the American Association of
14 Bovine Practitioners, American Association of Swine
15 Practitioners, and poultry pathologists. Do you have anything?

16 (No audible response)

17 DR. SUNDLOF: Robert, does that cover it?

18 MR. DODEMAIDE: (Nods head affirmatively)

19 DR. SUNDLOF: Then Tom Schilark spoke as representative
20 from the NCCLS. He indicated that a presentation should be made
21 by NCCLS to discuss the process in which they develop these
22 breakpoints for veterinary drugs, and maybe even some human drugs
23 should be presented at the workshop, as a way of bringing people
24 up to speed. Tom, was there anything else?

25 MR. SCHILARK: That was it. That was fine. .

1 DR. SUNDLOF: Okay. Patti Leiberman from CSPI.

2 Dr. Leiberman said that CVM needs to develop a sense of urgency,
3 pretty much was in agreement with the comments made by Richard
4 Wood that we didn't seem to be moving as fast as they would like.
5 There has been no response to CSPI's current citizens' petition.
6 The categorization she felt needed to be in place before we
7 entered into the discussion on setting thresholds. I had
8 something about the risk assessment, but I didn't put anything
9 down. Experts in public health, consumer groups, and EU policy
10 should be present at the meeting. That is all I had. Did you
11 have any addition?

12 DR. THOMPSON: Just a comment with regard to approval
13 of additional virginiamycin combination subs.

14 DR. SUNDLOF: Yes. Dr. Leiberman.

15 DR. LEIBERMAN: (Nods head affirmatively)

16 DR. SUNDLOF: Okay. Thank you. Dr. Al Sheldon from
17 Center for Drug Evaluation and Research at FDA supported European
18 experts -- by the way, let me just add that if you have names of
19 these European experts, please include those in the comments,
20 because that would be helpful for us. And that there should be
21 microbiologists from the FDA to provide information on how to set
22 interpretive criteria for breakpoints, that process,
23 understanding that process would be helpful in the discussion.
24 Al, did you have anything?

25 DR. SHELDON: No.

1 DR. SUNDLOF: Thank you. Then Dr. Fred Angulo from CDC
2 spoke. He indicated that there was a need for clarity on the
3 implementation dates that was also a theme carried out by -- or
4 that was expressed by Richard Wood and Patti Leiberman, and that
5 categorization would be helpful prior to the discussion on
6 thresholds, another issue that CSPI also spoke to. Got it?

7 DR. ANGULO: (Nods head affirmatively)

8 DR. SUNDLOF: Okay. Thanks, Fred. Then Joe Unowski
9 from CDER, FDA, indicated that categorization is genetically
10 linked to other antimicrobials and that some of the experts that
11 would be appropriate for the committee -- for the workshop at
12 least in December should be genetic experts to address this
13 issue.

14 MR. UNOWSKI: (Away from microphone) Right. I see that
15 as a risk factor.

16 DR. SUNDLOF: Risk factor.

17 MR. UNOWSKI: --- resistance also very ---.

18 DR. SUNDLOF: Again, if you know of people whose names
19 you could submit, we would appreciate that.

20 MR. UNOWSKI: Sure.

21 DR. SUNDLOF: Pre-approval workshop. Let me go back.
22 I think we got Dennis Wages. Dennis Wages representing AVMA and
23 AABP, Dennis?

24 (No audible response)

25 DR. SUNDLOF: The American Veterinarian Medical

1 Association and American Association of Bovine Practitioners,
2 with a comment from Eric Geinder, was that --

3 DR. WAGES: Yes.

4 DR. SUNDLOF: -- a separate comment. Okay. Let me see
5 if I can capture this. The AVMA commented that risk assessment
6 is essential to determine if there is any effect of regulation,
7 that is that unless you have done a risk assessment you will
8 never know if your efforts to regulate have been successful or
9 have any effect at all or made things worse. In addition, that
10 there needed to be a cost benefit analysis conducted, so that the
11 public understands the potential costs that restricting
12 antimicrobials would have versus any perceived benefits. So it
13 would be a risk analysis and a -- risk assessment and a cost
14 benefit analysis.

15 Small shifts in susceptibility may not have any effect
16 on increasing risk and that that needs to be taken into account.

17 Some experts that were suggested to come to the
18 meetings were Kathy Ewert from BARE and Dave Dargatz from USDA
19 AFSCIA.

20 Then I had that we needed to -- they needed some
21 clarification as to what the next steps should be, risk
22 assessment and threshold determination. Is there an acceptable
23 level of risk or is it zero, that was one of the questions that
24 was being asked; if it's a zero risk, then why are we talking
25 about this.

1 Then these are comments I am attributing to Eric
2 Geinder from here. Eric Geinder is a veterinarian who works both
3 for the turkey industry and the cattle industry, is that correct?

4 DR. WAGES: Swine. Turkey and swine.

5 DR. SUNDLOF: Swine.

6 DR. WAGES: Yes.

7 DR. SUNDLOF: Swine and poultry industry. He was
8 concerned about are we really doing a risk assessment or is this
9 risk reduction. I am not sure what the point was there, so maybe
10 Dennis can speak to that. Some experts suggested were Dr. Harley
11 Moon from Iowa State University and Dr. Lester Crawford from
12 Georgetown University. The question was raised whether managing
13 use in animals as we are proposing without taking commensurate
14 approach in human medicine makes any sense, that without a
15 parallel track on the human side he questioned the relevance of
16 taking any action on the animal side. Also, Clyde Thornsberry was
17 listed as an expert. There was some other information around
18 that, and I didn't catch all of that. On the pre-approval issue,
19 well, we'll get to the pre-approval issue later.

20 DR. THOMPSON: The only other thing, and I wasn't clear
21 if this was relating to pre-approval, was on -- he recommended
22 collecting samples from -- rather than on-farm, I understood from
23 pre-packaged food.

24 DR. SUNDLOF: And then ---.

25 DR. WAGES: (Away from microphone) --- pre-approval.

1 DR. THOMPSON: Pre-approval.

2 DR. WAGES: I will submit these to you --

3 DR. THOMPSON: Okay.

4 DR. WAGES: -- because it's in writing, as they were
5 written. So, because I was just some kind of messenger.

6 DR. THOMPSON: Okay.

7 DR. WAGES: ---

8 DR. THOMPSON: Okay.

9 DR. SUNDLOF: Okay. Well, yes, we just want to make
10 sure everybody is in agreement on what we heard today. I am
11 going to move over to -- unless there are additional comments,
12 I'll move over to the pre-approval summary, pre-approval workshop
13 summary of the comments.

14 Again, Dr. Carnevale from the Animal Health Institute
15 spoke on this issue. He asked that we state the purpose for pre-
16 approval studies, that we make it very clear why it is that we
17 want pre-approval studies and what those studies are an attempt
18 to provide us in terms of information that will be helpful in
19 making a safety assessment.

20 Now, how will they be used in evaluating, how will
21 those pre-approval studies actually be used within the regulatory
22 process for evaluating new animal drug applications. He thought
23 that in terms of the experts that we should have, there should be
24 presentation by people who have experience with the 55815 studies
25 and their value. In other words, we have required some pre-

1 approval studies for certain continuously fed antimicrobials in
2 feed, and those studies, get people involved who have got
3 experience in there, tell us where the strengths and the
4 weaknesses of that approach has been over time.

5 Then an overview of the animal drug development process
6 and a separate talk on -- that talks about from discovery to
7 actual approval and marketing of the product and what all is
8 involved in that, to give people a sense of the amount of effort
9 that goes into that. Does that pretty much capture it, Rich?

10 DR. CARNEVALE: (Nods head affirmatively)

11 DR. SUNDLOF: Okay. Thank you. Then Richard Wood from
12 Food Animal Concerns Trust said -- is concerned that pathogen
13 load needs to be a part of the discussion and that whether it's
14 in conjunction with the February meeting or at another meeting,
15 it's an important issue and it needs to be addressed.

16 He again considered that we need to make sure that we
17 are progressing in a timely manner, that it is an urgent issue
18 for FDA and that we take it as such.

19 Finally, he asked the question of post-approval
20 monitoring, where is it covered in the workshop, and that this is
21 an issue that needs to be addressed. I think that is all I have.
22 Richard, was that --

23 MR. WOOD: (Away from microphone) Yes. Just one
24 additional comment that really wasn't a prior comment I made. I
25 don't know if you called ---, and that had to do with the

1 process, the meeting process for both workshops. I think what I
2 was driving at anyway is that if it is a round table format, that
3 it not end at the round tables, that there be, perhaps with
4 Dr. Carnevale's model, a final plenary or some session where
5 there is a full table with discussion around that full table
6 among all concerned parties.

7 (Pause)

8 DR. SUNDLOF: Okay. Yes. I was just consulting with
9 Dr. Thompson to make sure I have the next steps right. We will
10 keep the docket open. We do welcome everybody's comments. We
11 will try and take what we've learned here today and summarize
12 those and include that in the docket. Based on your comments,
13 this will help us as we move forward to planning the meeting in
14 December, and we will, I know we said this before, we will try
15 and get the information out to you just as soon as we can.
16 Again, this is the top priority for CVM. Resources are strained
17 as it is, but we will do whatever we can to get both the risk
18 assessment out and further information on this meeting out just
19 as soon as possible. Once again I want to thank everybody for
20 coming here today and participating in this important meeting.

21 (Whereupon, the meeting was adjourned at 3:30 p.m.)
22
23
24
25

Appendix

Dr. Richard Carnevale

**Comments of
Animal Health Institute**

**Before the
CVM General Public Meeting
Rockville, Maryland
October 4, 1999**

I am Dr. Richard Carnevale, Vice President of Scientific, Regulatory and International Affairs for the Animal Health Institute. On behalf of the Animal Health Institute and its member companies, we appreciate the opportunity to appear before you today to provide our views on CVM's upcoming workshops on risk assessment and the establishment of resistance thresholds, and pre-approval studies in antimicrobial resistance. In addition to our brief comments today, AHI will provide written comments, which will include suggestions for topic specific experts.

AHI recommends a workshop format that provides the participants with a briefing on the critical issues impacting and influencing the topics under discussion followed by breakout sessions to examine simultaneously multiple topics by appropriate experts, and a closing session for bringing together the various elements. Additionally, we would encourage CVM to begin each workshop with a clear statement of the purpose of the workshop; what they envision as the end product of the workshop; and what the next steps will be after the conclusion of the workshop.

Risk Assessment/Thresholds Workshop

AHI believes a general discussion of the application of and differences between risk assessment and risk management would be an important introductory session to be addressed in the plenary. Another key topic for the plenary is in the area of microbiological breakpoints and how they are usually determined and used by the medical community.

AHI further recommends the following topics for discussion by experts and workshop participants during breakouts.

- An analysis of the components of the CVM risk assessment model and how probability estimates have been applied to the populations at risk.
- A discussion of the use of in vitro sensitivity data and breakpoints as reliable indicators for predicting human health impact.
- An examination of how to define both a monitoring and a resistance thresholds and how they would be evaluated and enforced.
- A discussion of possible mitigation steps if a threshold is reached.
- Since a risk assessment is a dynamic process, a discussion of how ongoing changes could be evaluated and incorporated into the risk assessment model, including how the model might be applied to existing products.

- A review, including both policy and legal issues, of the application of the standard “reasonable certainty of no harm.” We believe this is a critical discussion since this standard is the foundation for setting thresholds. We believe there are valid questions as to whether this standard, as applied to the approval process, is properly applicable to actions the FDA may take in attempting to control antimicrobial resistance.

Pre-Approval Studies Workshop

Our comments on this second workshop will be limited in scope at this time. However, we have already commented extensively on this element in our comments on the CVM Framework Document. For your convenience we have attached our comments to our written statement.

AHI would encourage CVM to include in a plenary session a discussion of the purpose of the proposed pre-approval studies and how these studies will be used. We believe it would be beneficial to have an expert discuss the microbiological studies currently required under 21 CFR 558.15 for “continuous use” antimicrobials and what has been learned from them. We also believe that it would be informative to outline the steps that are followed in bringing a veterinary product from the discovery phase through the approval process in order to provide a more comprehensive picture of what goes into the evaluation. AHI would be happy to nominate a company expert to provide this briefing.

Alexander S. Mathews
President & CEO

April 5, 1999

Dockets Management Branch
Food and Drug Administration
12420 Parklawn Dr. (HFA-305)
Rm. 1-23
Rockville, Maryland 20857

Re: Comments to FDA Docket No. 98D-1146, "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals."

The Animal Health Institute provides these comments to the document released by FDA in December 1998 and reviewed by the Veterinary Medicine Advisory Committee in a meeting held by the agency on January 25-26, 1999.

AHI is a national trade association representing manufacturers of animal health products – pharmaceuticals, vaccines and feed additives used in modern food production and the medicines that keep pets healthy.

The animal health industry shares the concern with FDA for the potential development of antimicrobial resistance from the use of antimicrobial drugs in food animals and appreciates the detailed consideration the agency has given to this matter in the proposed framework document. However, the proposed regulatory approach constitutes a significant change in the way the agency intends to evaluate new animal drug applications for these products that would have serious negative consequences for animal agriculture without any significant impact on reducing the problem of antimicrobial resistance in human medicine.

As it stands, the proposed Framework would have the potential to severely limit existing antimicrobials and restrict the approval of new products. Additionally, the extensive new requirements envisioned in the proposed Framework would effectively prohibit companies from committing the resources necessary to develop new products. The effect would be unintended negative consequences on animal health, animal welfare and the risk of sending unhealthy animals into the food chain. Healthy animals help ensure a healthy and safe supply of meat and poultry for consumers.

While we work to sort out the complexities of the Framework proposal, we acknowledge that this is an urgent issue and recommend that some immediate actions be undertaken. This includes:

- 1) agreeing to continue to fund and provide additional support to enhance the current NARMS program so that it can fulfill all the requirements for post-approval data;
- 2) assembling experts representing the necessary areas of expertise such as microbiology, epidemiology, biometrics and risk management. These experts could address the complex issues identified in the proposed Framework dealing with categorization, pre-approval studies, thresholds and post-approval monitoring;
- 3) undertaking a risk assessment to determine the real risk to public health to ensure any regulatory changes are proportional to the true scope of the problem.

Further, as recommended by the VMAC, FDA/CVM should resume the approval of new antimicrobials in the review pipeline under the existing, rigorous regulatory guidelines as new regulations are being developed.

AHI is willing to work cooperatively with FDA/CVM to develop a scientifically sound and lasting approach to the approval process for new antimicrobials that leads to a safe food supply and a flow of new products to solve the medical problems of the livestock industry while being protective of public health.

To that end, in developing AHI's comments, considerable effort on the part of industry scientists has been put forth in evaluating both the conceptual and contextual aspects of the proposed Framework. In addition, AHI has enlisted the aid of expert consultants in the areas of epidemiology, microbiology, resistance development and monitoring as well as risk assessment to help evaluate the proposed Framework. Based upon this review, AHI does believe there is common ground on which we can move forward and as such, provide detailed comments in the attached document.

Sincerely,

Alexander S. Mathews

Attachment

Comments to FDA docket number 98D-1146
**“A Proposed Framework for Evaluating and Assuring the
Human Safety of the Microbial Effects of Antimicrobial New
Animal Drugs Intended for Use in Food-Producing
Animals”**

**Prepared by
Animal Health Institute**

April 5, 1999

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I. The Link between Antimicrobial Resistance in Foodborne Pathogenic Bacteria and Use of Antimicrobials in Food-Producing Animals

Much of the proposed Framework Document is devoted to providing justification for the stated need to evaluate microbial safety of antimicrobials intended for use in food-producing animals. This justification is based on the assumption that use of antimicrobials in food-producing animals plays a significant role in selecting for resistance in foodborne pathogens that consequently may be passed to humans and adversely impact public health.

At the FDA Veterinary Medicine Advisory Committee meeting held January 25-26, 1999, it was pointed out by a number of industry and professional organizations that, while it is agreed there is potential risk, the actual magnitude of this risk has not been determined. Therefore, it was the recommendation of these groups to establish an appropriate risk assessment methodology to quantify the potential impact of food-animal antimicrobial use on human health. It was further suggested that the outcome of such a study should then be used to help determine what, if any, additional measures should be enacted to protect the public health. AHI still believes this is an essential first step in order to avoid serious over regulation of an already highly regulated industry.

In justifying the need for further regulation, the Framework Document discusses the development of resistance as the direct result of antimicrobial use. It also discusses the fact that bacteria can become resistant indirectly when resistance traits are passed on from other bacteria by mechanisms that allow the exchange of their genetic material. A number of references are cited to support both the direct and indirect acquisition of resistance. In the following subsections, comments are provided on the evidence used to support these concepts and their relevance to a public health threat.

Direct Transfer of Resistance

In the introduction to the framework proposal, CVM claims that new reports, particularly from Europe, have rekindled concerns about the contribution of animal antibacterial use to development of resistance in food-borne bacteria. Several literature references have been cited to support their conclusions that immediate action is necessary by the agency to change the regulatory approach to the approval of antibacterials in food producing animals.

One of the key reports referenced in the document is that of Threllfall, *et al*, from the Central Public Health Laboratory in Great Britain published in 1996. In a series of articles the authors suggest that temporal increases in “resistance” levels of *Salmonella typhimurium* DT104 are directly tied to veterinary use of fluoroquinolones. This and other reports from this laboratory were what the industry viewed as the trigger that set the agency on the current path to propose sweeping changes to the regulatory process. And while we viewed this as important new information regarding an emerging food-borne threat, we did not believe that the information was sufficient to cause such a significant disruption to the approval process for veterinary drugs.

First, the term "resistant" has been used by the authors not to describe clinical resistance, but rather a shift in susceptibility. They have chosen lower breakpoints than the standards set by the National Committee for Clinical Laboratory Standards (NCCLS) and the British Society for Antimicrobial Chemotherapy (BSAC). What have been reported as "resistant" isolates are, in reality, clinically susceptible according to NCCLS and BSAC guidelines.

Second, there is no documented case of a human fluoroquinolone treatment failure of DT104 because of resistance caused by an animal drug use.

And, third, reports from that same laboratory over the last two years demonstrate a marked decline in the incidence of *Salmonella typhimurium* DT104 with no clinical resistance to the fluoroquinolones. At the same time, the percentage of those isolates have shown no change in susceptibility from the previous year.

Another study published in 1991 concerns fluoroquinolone resistance levels in *Campylobacter* spp. in poultry in the Netherlands. This information was considered by the 1994 FDA Joint Advisory Committee prior to its recommendation that fluoroquinolones were approvable for therapeutic use in food animals. The Advisory Committee did not consider the Netherlands experience adequate evidence to establish a public health risk that would preclude the approval of quinolone animal drugs in poultry. For one thing, a high level of resistance was already present in *Campylobacter* prior to the introduction of fluoroquinolones for use in poultry.

The conclusions of the study in Spain, where increases in resistant strains of *Campylobacter* spp. were observed, is complicated by the fact that manufacturing and distribution of fluoroquinolones and other veterinary and human pharmaceuticals are generally less controlled in that country. In particular, these products tend to be more readily available for human and animal use in contrast to the limited and veterinarian controlled uses in the United States. This report also fails to demonstrate a direct link between fluoroquinolone use in animals and development of resistance in people.

The reference cited from the Minnesota Department of Health has yet to be published; however, much of this *Campylobacter* data has been reported at various meetings. From the information presented to date only a small percentage of the human clinical cases were associated with a fluoroquinolone resistant *Campylobacter*, and the majority of these were attributed to foreign travel. It has further been reported by the same author that fluoroquinolone resistant *Campylobacter* has been increasing in human isolates since 1991, four years prior to the approval of any fluoroquinolone in food-producing animals.

Indirect Transfer of Resistance

The Framework Document points out concern for development of antibiotic resistance in enteric bacteria that may, under certain circumstances be pathogenic. References are appended from several studies in Europe, which suggest a link between vancomycin resistant enterococci and glycopeptide use in animal feeds. These references are part of a significant research effort in Europe to incriminate the use of antimicrobial growth promoters as being responsible for

transferring resistance to humans. These and other studies have been considered by the Scientific Committee on Animal Nutrition, an advisory body to the EU Commission. They have reviewed the situation with several drugs, namely avoparcin, virginiamycin, tylosin, and spiramycin. In every case their conclusions have been that the data falls short of being able to conclude that use of these drugs in animal feed represents a significant public health risk.

The proposed food animal enteric reservoir as a direct transfer link to humans is often postulated as a significant mechanism for antibiotic resistance emergence. Recently (1999), European Union authorities banned four useful antibiotic-based feed ingredients, based largely on public health concerns related to the reservoir-transfer hypothesis. A literature base supporting this hypothesis is frequently referred to in reviews and in regulatory publications (1,9,37).

Reviewing the literature base more holistically, however, one may also conclude that the hypothesis is questionable as a major risk to public health. There are other reviews that are usually not considered in written pieces favoring the reservoir-transfer hypothesis (7,8,12,19,20). Research and empirically based evidence suggests that animal-to-man resistance transfer is not a major ecological pathway for emerging resistance in human pathogens. Recent letters to the American Society for Microbiology's ASM News have pointed out these concerns (21,22). This review is intended to provide more complete information and to cover material that is often not included in the numerous reviews, papers, letters, and forums that emphasize the reservoir-transfer hypothesis as a public health concern.

Further, a report entitled *Human Health and Antibiotic Growth promoters (AGP): Reassessing the Risk* was recently released by the HAN foundation (Heidelberg Appeal Nederland), an independent alliance of scientists whose aim is to ensure that decisions are taken based on sound scientific principles (40). The report, based on a comprehensive review of over 3000 cited references, concluded that convincing data on the transfer of resistance from animals to humans is clearly lacking. The report also found that past experiences with the use of antibiotic growth promoters do not reveal that they are a major source of resistance within human bacteria even after 30 years of use. Moreover, there are no indications that human infectious diseases are on the increase as a result of the use of antibiotic growth promoters. These findings were presented and accepted at a European Scientific Conference entitled "The Use of Antibiotics in Animals – Ensuring the Protection of Public Health" held at the headquarters of the Office International des Epizooties (OIE) in Paris from 24-26 March 1999.

As it relates to gram-negative enterics, many studies have been published that have demonstrated transfer of R plasmids possessing single or multiple resistances *in vitro*. A small set of papers address the issue of animal-derived enterics (3,13,25,26,32), and a smaller subset demonstrated transfer *in vivo* (10). Among these enteric transfer studies, however, the test microorganisms were either mated at high cell densities under optimal lab conditions or *in vivo* inoculated into the animal at high cell densities of model donor/recipient bacteria. Authors caution about extrapolating the *in vivo* studies as being representative of actual conditions. It is highly improbable that within normal production systems, animals would be concurrently inoculated with massive numbers of drug-resistant donor and recipient bacteria. What is left is the possibility that normal enteric flora may interact with potential human pathogens within food

animals. Whether the normal range of enteric load, environmental and nutritional factors, or antibiotics greatly enhances this possibility is still a subject of research.

Another possibility is that animal-to-man resistance transfer may occur over longer time frames. This could render foodborne pathogens more resistant in the long run, eventually leading to increased resistance frequencies in human pathogens. There is a body of recent evidence that suggests otherwise, however. Lorian (19,20) reported on the susceptibilities of about 2 million *E. coli* and 19,200 *Salmonella* strains over a nine to eleven year period. Most drugs demonstrated a steady state in the percentage of susceptible strains. Lorian gave the example of tetracycline; resistance to tetracycline in human strains did not increase (in fact it decreased somewhat). Despite routine use in food animals, there was no corresponding increase among human clinical isolates. He therefore concluded that tetracycline use in animal feeds was not effecting the resistance levels of human isolates. Seven other clinical human pathogens were also tested for resistance to a battery of antibiotics showing the same pattern, giving an indication that this effect is not limited to *Salmonella*.

To expand on Lorian's study, we can compare the results with a more recent national survey (2). Table 1 is a summary of the average values of percent resistance for *Salmonella* isolates. Antibiotics common to both Lorian and NARMS surveys are shown. There is a surprising similarity in the averages reported in both studies. The values reported by NARMS in 1996 and 1997 for *Salmonella* generally lie within or close to the ranges reported by Lorian. If one considers *Salmonella* to be an important sentinel organism, and tetracycline as representative of feed antibiotics, then we can not conclude that food animal tetracycline usage has caused a significant change in overall resistance in human pathogens, using two nationwide surveys as evidence.

Table 1. Comparison of Lorian and Recent NARMS National *Salmonella* Survey Data. Values expressed as Percent Resistance (rounded).

Antibiotic	Lorian Survey:	(Range)	NARMS Survey:		Veterinary* 1997 (n=2391)
	Human 1975-1984 (N=19,200)		Human 1996 (N=1326)	Human 1997 (N=728)	
Ampicillin	17	(14-24)	21	20	12
Tetracycline	22	(18-31)	24	23	27
Cephalothin	10	(7-17)	7	9	2
Chloramphenicol	4	(2-6)	11	11	5
Gentamycin	1	(1-2)	5	4	6
Nalidixic	6	(5-30)	0.4	1	1
Trimeth./Sulfa	4	(3-7)	4	2	2

*Averages compiled from eleven species and sources, both clinical and non-clinical

This data provides more retrospective evidence to the view that the earlier proposed ban on tetracycline and penicillin use in feeds was probably not justified as U.S. national policy. Chloramphenicol resistance appears to have increased among human clinical isolates using Table

1. This drug has not been used in food animals in more than ten years. Interestingly, there was significant nalidixic acid resistance during the 1970's and 1980's, putting more recent NARMS data perhaps into greater context in regard to concerns about a linkage to fluoroquinolone resistance emergence among *Salmonella* species.

Animal studies have shown that the ratios of antibiotic resistant enteric flora decline slowly and not completely after the removal of all antibiotics. Pigs in the Langlois study (16) showed a shift of only 94 to 53% tetracycline-resistant coliforms after fourteen years of no antibiotic exposure. Application of a stress factor (loading and transportation) caused the resistant population to jump back to 82%. A single course of chlortetracycline raised the coliform resistance levels to that of control herds which received the drug for 13 years. The antibiotic-deprived herd further showed erosion of performance values and higher endemic infection. Sogaard (33) reported 74% *E. coli* resistance in pigs given therapeutic antibiotics, versus 53% in pigs given no antibiotics. Similar results were reported by Gellin, et. Al (11). These numbers are consistent with the NARMS 1997 *Salmonella* data from swine (50% among HACCP and 75% among clinical isolates). The NARMS data showed a wide range of percent resistance among total isolate sets from different animals (14 to 57%). From this wide range of resistance, it can be anticipated that even extensive on-farm testing of food animals' enteric flora would be very complex to interpret in evaluating or managing potential risk for antibiotic resistance transfer to human pathogens.

A significant amount of evidence shows that animal species barriers are generally respected among intestinal colonizing flora (excluding the direct foodborne pathogens *Salmonella* and *Campylobacter*). Nijsten performed a detailed study of farmers and pigs in the Netherlands, and concluded that there was not a common pool of *E. coli* resistance strains or plasmids that colonized both farmers and their herds, even among strains having the same resistance profiles (26). Similarly, O'Brien, et. Al. Showed that *E. coli* plasmids derived from poultry carcass isolates and from abattoir worker urinary tract infections were not related. There was a separation of plasmid relatedness among the poultry isolates, depending on the source of the birds (27). A paper by Kariuki, et.al. studied *E. coli* isolates from chickens and children in close contact with the birds, by pulsed-field gel electrophoresis (PFGE). The study showed that although several genotypes were present, the *E. coli* from the two sources were distinct (14).

The conclusion from these studies is that the ability of most animal-derived enterics to directly colonize human intestines and transfer resistance elements within humans is limited. This is in contrast to earlier reports suggesting that a common pool of enteric strains and resistance factors exist in humans and animals (17,18). The earlier studies actually showed that a limited and short-term human colonization is possible. In terms of relative contact time and optimal transfer conditions, however, the same arguments mentioned earlier for *in vivo* transfer studies apply. The more recent occupational exposure studies would be expected to demonstrate extensive direct transfer and colonization were it an important mechanism for resistance development in humans. It seems unlikely; therefore that food animal-derived enterics could be an important source of resistance transfer to humans by the food supply.

Bates, et.al. is frequently cited as evidence for farm animals as a putative reservoir for vancomycin-resistant enterococci (1,9). Interpreting some of the data in this paper, however, one

can also make the following observations: a) non-food animals routinely harbored vanA enterococci, b) the majority of animal and clinical isolates had different ribotypes, and c) the one common ribotype that was found was not associated with acute hospital infection. Van Den Braack et.al. demonstrated significant differences between vancomycin-resistant enterococci from poultry products and from hospitalized patients in the Netherlands using molecular techniques (34). Klein, et.al. demonstrated relatively low levels of VRE in minced meat products in Germany, and the resistance patterns were different from clinical isolates. A connection between the occurrence of VRE in minced meat and nosocomial infections could not be demonstrated (15). Butaye, et. Al. Demonstrated that the isolation of glycopeptide resistant enterococci from pigs and chickens is highly variable, dependent on the type and age of animals and the isolation techniques used. These factors were exclusive of glycopeptide use as the study was done after the 1997 bans on avoparcin in Europe (6).

Research in the food and environmental microbiology areas are also important to the reservoir-transfer hypothesis. One study demonstrated that resistance transfer could occur *in situ* in meat-derived *E.coli* (13). Another study showed the inability to transfer antibiotic resistance in *E. coli* on meat surfaces, however (23). Cheese and dairy microorganisms can harbor and transfer antibiotic resistance plasmids and transposons (28,29), as well as bovine mammary staphylococci (24). Human exposure to these microorganisms could therefore also be potentially significant to public health, as they are routinely consumed at high volumes (in contrast to meat-derived enterics, which must bypass processing and cooking gauntlets), and could potentially transfer resistance to human pathogens. Soils are known to possess numerous bacteria that harbor (and can transfer) antibiotic resistance, even soils with no specific selective pressure (5,25). Probiotic bacteria have also been cited as potential hazards to immune compromised individuals based on their potential to harbor and transfer resistance elements (36). Non-meat foods have been implicated in several *Salmonella* outbreaks (7,8), suggesting that vectors other than food animals are important to human enteric pathogen transfer. A recent pediatric study explored the role of contaminated foods in homes versus numerous environmental factors. The conclusion was that contaminated foods in the home played a less significant role in *Salmonella* infections of infants and children (31). Erythromycin sensitive cutaneous staphylococci re-established their ecological niche shortly after cessation of topical therapy with the drug (35). This demonstrated an example of the re-colonization by susceptible flora after antibiotic treatment. Even surface water is found in some cases to contain antibiotics, another selective environment that could influence the ecology of resistance development (30). These examples from the food and environmental research fields demonstrate the complex and dynamic nature of resistance development and recession.

In conclusion, the reservoir-transfer hypothesis as applied to food animals and antibiotic usage is based mostly on speculative concerns, limited studies, exceptions to the rule, and presumptive epidemiological associations, not the complete literature available on the subject. The fact that plasmid transfers can occur *in vitro* and *in vivo* under high density optimized model test systems does not equate to such events being common in typical production settings. Multiple factors besides antibiotic usage can contribute to conditions that increase the relative amount of resistant enteric bacteria. Additional evidence points to bacterial strains and plasmids generally respecting species barriers even among individuals with daily occupational exposures. Resistance frequencies of enteric pathogens for most antibiotics have shown remarkable stability

for over three decades of concurrent veterinary and human antibiotic use. Sources for resistance selection and potential transfer to human enteric pathogens are not limited to the meat production chain. Only if solid correlation can be made between human clinical pathogens and food animal-derived enteric flora associated with antibiotic use, can the reservoir-transfer hypothesis be considered a significant mechanism. Caution is suggested in applying *a priori* precautionary solutions. The downside of applying more restrictions to properly used animal antibiotic products could be an actual increase in total zoonotic pathogens due to their not being under control (12, 22) from a lack of suitable alternatives to the animal drug. The positive role of antibiotic based products to animal health and safer food supplies should not be underestimated, nor the risks overstated.

There is no question that common resistant isolates or resistant determinants can be found in humans and animals as a result of antibiotic use. Clearly, animals and humans can exchange bacteria carrying these properties. However, the cited evidence, in our view, does not rise to a level which justifies the extreme measures being proposed by CVM.

New Human Antibiotics

CVM uses as part of its justification for imposition of the new requirements outlined in the Framework Document the lack of new classes of antibiotics for human therapy. A recent review indicated that at least seven new antimicrobial classes are in various stages of development. Most appear to be semisynthetic derivatives of known antibiotics with one unique class of antimicrobial agent having been discovered (38). This would seem to contradict the predictions of a dire emergency from the lack of alternatives to currently available antimicrobials, since FDA can expedite the review of important new drugs.

Although AHI questions the basis for the proposed framework, based on the foregoing analysis, we have reviewed each of the individual concepts in the document and continue our remarks with the following:

II. Categorization

According to the Framework Document, CVM proposes to categorize antimicrobial compounds intended for use in food-producing animals based on the importance of their chemical class to human therapeutics. In particular, Category I is intended to include drugs that are in the same chemical class as drugs that are **essential** for human therapy, and **no** alternative therapy exists. Drugs that induce cross-resistance to Category I drugs also would be classified as Category I. Drugs considered to be in Category II would include members of a chemical class that are **important** for human therapy, but for which **satisfactory** alternative therapy exists. Drugs that induce cross-resistance to Category II drugs also would be classified as Category II. Drugs considered to be Category III would include those in a chemical class that is not of importance for human therapy.

CVM proposes to further categorize new compounds based on their ability to result in exposure of humans to antimicrobial-resistant human pathogens. *High* exposure includes drugs that are administered for an extended period on a flock or herd-wide basis. *Medium* exposure includes drugs intended for the control, prevention, mitigation or treatment of disease conditions where use duration is between 6 and 21 days. *Low* exposure includes drugs that are intended for the treatment of a small percentage of a flock or herd for a period of less than 6 days.

With respect to the importance to human therapeutics, it is important to realize that for a new chemical entity, much of the data on which categorization is based is not available. Consequently, it must be assumed that most (if not all) new animal antimicrobial drugs would be assigned to Category I. A mechanism would need to be defined by which the drug will be reassigned to a lesser category, as data (and perhaps newer human drugs) become available.

Likewise, if this system were implemented, category assignments for approved animal antibiotic classes should be immediately established. A wealth of epidemiological data indicates that existing animal drugs do not pose a human health threat due to the transfer of antimicrobial resistance, thus the levels of resistance which currently exist could be regarded as safe.

Essentially, Category I drugs are those that only would be used in animals if a clear indication exists, and **no** evidence for resistance among **zoonotic pathogens** is observed. The most immediate danger of such a categorization scheme would be to compel pharmaceutical companies to take a conservative approach to new product development, and divert resources from innovative programs to duplicate existing products that have been established as Category III and thus, are more likely to be approved expeditiously. *This situation would result in the virtual elimination of novel therapies that are urgently needed, while increasing the selective pressure for the emergence of resistance to drugs currently available.*

Additionally, the Framework Document includes terms that lack a clear definition. For example, the term "cross resistance" must include contextual information as to the methodology employed to evaluate and the specific bacterial species used (*i.e.*, zoonotic vs. human, pathogen vs. commensal, target species vs. surrogate). Presumably, surveillance of zoonotic as well as human pathogens would be done, for comparison (and to document that an MIC shift in a human

pathogen has no counterpart among zoonotics). The criteria on which an alternative therapy is judged to be “satisfactory” also needs to be defined.

The Framework Document also needs to acknowledge that genetic changes in bacteria occur in the *absence* of selective pressure by *any* antibiotic. Accordingly, a defined procedure is needed that describes the criteria by which a shift in MIC among human pathogens is attributed to transfer from zoonotics that was induced by exposure to a particular antimicrobial.

With respect to the exposure of humans to antimicrobial-resistant human pathogens concern was expressed for direct transfer of resistant zoonotic bacteria as well as resistance transfer to susceptible human bacteria. There are sufficient data indicating that zoonotic bacteria rarely colonize human hosts (except for acute colonizations by *Salmonella*, *Campylobacter*, and other direct food borne pathogens). Several recent publications show that different strains and plasmids colonize humans and farm animals. Even strains with apparently similar resistance profiles were found to have different biotypes and plasmid patterns. Humans with daily or occupational exposures to zoonotic bacteria such as *E. coli* rarely develop infections from animal strains. The opportunity for contacts of human and animal enteric bacteria leading to transfer events is, therefore, limited. The concerns related to horizontal transfer from extrachromosomal elements are recognized. There are, however, too many unproven points of origin and bacterial species barriers for this mechanism to be considered a primary mode of transmission related to antibiotic usage in animals.

A troubling aspect of the Framework Document is the lack of scientific balance by inclusion of references that support the Agency’s point of view to the virtual exclusion of those which argue otherwise. Experts do not agree about the relationship between the extent of antibiotic exposure (*i.e.*, dose or duration) and the rate of resistance emergence for a particular bacterium. The pharmacokinetic/pharmacodynamic properties of individual products should be considered when attempting to predict the relative selective pressures that might be imposed. Furthermore, there are many factors in addition to usage levels, such as aqueous solubility, particle size, excipients, etc., which determine the actual concentration to which the bacteria are exposed (*i.e.*, the microenvironment). These considerations could be more important to the potential for emergence of resistance than the duration of treatment.

By including an estimate of the route and duration of use for a new antimicrobial compound in the categorization scheme, pharmaceutical companies again will be compelled to develop products that are likely to be approved expeditiously. Since practicality dictates that antimicrobial drugs for poultry and swine are administered to an entire flock/herd, it is expected that these products would be categorized as high-exposure according to the Framework Document. Consequently, the development of new products for these species likely will be compromised, in favor of products that would be considered medium- to low-exposure.

Studies to assess the selective pressure of a single antimicrobial may not be predictive of the actual pressure that might occur under actual conditions of use. In food animal medicine, antimicrobials are frequently used concurrently. Recent modeling studies suggest that simultaneous uses of different antimicrobials at the population level as well as combinations of antimicrobials are more optimal strategies for minimizing the emergence of antimicrobial

resistance (39). These models suggest that the long-term benefit of a single drug treatment from introduction until a high frequency of resistance would preclude its use is almost independent of the pattern of antibiotic use.

Specific Recommendations

The Animal Health Institute believes that categorization of new antimicrobial drugs intended for food-producing animals has merit. For the reasons discussed above, it seems most plausible to establish two broad categories of antibiotic classes: **those of importance to human medicine and those that are not important.** However, it is critical that appropriate parameters and criteria be developed to ensure a continued transparent, predictable and science based regulatory process that industry depends on.

Furthermore, because the number of animals exposed to an antibiotic (*i.e.*, high – medium – low) does not relate to potential exposure of humans to foodborne pathogens, this consideration should be eliminated from the categorization scheme.

III. Pre-Approval Studies

Animal Studies Pre-Approval

The Framework Document outlines two types of studies to be done in animals. The first is to characterize the nature of resistance development (*i.e.*, rate and extent) and the second is the pathogen load study. It is not clear whether one study could suffice to meet both objectives or whether multiple studies will need to be conducted. Within each study, mitigation measures are to be tested as well. Regardless of the type of study, certain fundamental design aspects need to be clarified.

Organisms of Concern

Are the organisms “of concern,” the same for both the antibiotic resistance and pathogen load studies? What exactly are the enterics or pathogens of concern (all 3 of *Salmonella*, *Campylobacter* and *E. coli*; or 1 or more of these dependent on the animal species; or any G+ or G- enteric, or enteric bacteria such as enterococci that *might* be capable of transferring resistance to human pathogens)?

If the organisms of concern are the same for both the antibiotic resistance and pathogen load studies, could one study address both issues? If multiple types of enterics or pathogens are to be studied, can/should they all be studied simultaneously in the same animal subjects?

Are there bacterial genera or species or even specific types (*e.g.*, definitive type DT104 or antigenic type O157) that are required to be studied? In addition, should any one or more of salmonella species known to comprise at least X% of human clinical cases be tested?

It must be recognized that a multitude of different bacteria resides at different densities throughout the intestinal tract of animals. This complex ecosystem cannot be dissected into a bacterial species-specific experimental design.

If a separate study is required for each foodborne pathogen, the complexity and practicality might preclude sponsors from developing new agents requiring several of these studies.

Target Animal

Is the “target animal” strictly defined as one that is in the clinical condition that the drug of interest would be used on? That is, if it is a therapeutic product candidate intended for use against a swine respiratory disease, are the target animals those which are in said disease state? Or should healthy animals, which are unlikely to have the product used, be chosen? Should the animals be young or near slaughter weight (see discussion below)?

If particular enteric foodborne bacteria are to be studied, are these organisms to be studied from those found in naturally occurring, field situations of clinical or non-clinical

(carrier) animals? If so, farms must be identified as to their foodborne pathogen status (and possibly their target pathogen status as above). This in itself would be a major epidemiological undertaking as factors such as new animal acquisition, weather, diet, need for antibiotic treatment, etc., can affect the status of the farm. Since by definition these farms would have a “problem” with foodborne pathogens, there may be inherent problems with management, etc., which preclude their use in a carefully controlled study. Of those farms so identified, what frequency of isolation, number of animals, and types of controls would be required to determine any effect by an antimicrobial? Or, is the expectation that pathogen studies will be performed in controlled trials wherein subject animals have been artificially/experimentally colonized with the pathogen(s)? If so, how does such a model correlate to the field situation?

It is also unclear as to how many such studies would need to be conducted, the statistical power and design required (*e.g.*, animal vs. pen; animals per pen; herd/flock numbers), as well as other study parameters (clinical observations, feed intake, etc.).

Drug Exposure

Since the studies are to be conducted pre-approval, issues related to the condition of the drug candidate need to be defined. Is the use of clinical trial material (*i.e.*, final formulation, certified analytical grade active) required? Manufacture of this type of test article is a major commitment by the sponsor because it means that the factory, analytical assays, stability, and formulation issues have all been resolved. Since the types of studies to be required by the Framework Document will be of uncertain outcome, and, therefore of high risk from a business standpoint, consideration must be given to the type of material required.

Until the issue of target animals is addressed, issues on drug exposure remain to be defined. For example, in a field exposure situation, treatment begins at or near the time clinical disease signs are evident and, in this scenario would need to be overlaid on top of the enteric pathogen presence. If apparently healthy, but foodborne pathogen colonized herds or flocks were used instead (*i.e.*, no superinfection with a target disease pathogen) the issue is when should the drug be administered. In a model system, the enteric pathogen challenge dose is usually given, and immediately followed by drug administration.

If there are multiple allowable dosage regimens, or an allowed dosage range, what is considered the “highest exposure scenario?” That is to say, would a one-time dosage of 500 mg be considered a higher exposure than 3 of 250 mg dosages, q.o.d. or vice versa? In historical 21 CFR 558.15 studies, the highest permissible dosage was the only dosage required to be tested. Is the “highest exposure scenario” always considered as “covering” the lower exposure usage(s) so that those dosages need not be studied?

An interesting case to be addressed is that for antimicrobials that are broad spectrum. It is possible that the foodborne pathogens of interest could be eliminated by the treatment. In this case it would be reasonable to expect perturbations of gut microflora with some selection pressure for resistance in the remaining “bystander” enteric bacteria in the course of eliminating the target pathogen, particularly if the product is to be orally administered. It is quite possible that by the time the animal has reached market weight, the gut flora changes have returned to

baseline. In this case, how will the study be interpreted? If all is “normal” at slaughter, is the intent to use the time to return to pre-treatment baseline as a microbiological withdrawal period?

Points in Time

What are the most relevant points in time that the bacterial organisms need to be studied; *i.e.*, is time of slaughter the only truly relevant time? Or is time of slaughter the key time, but studied animals should have been exposed to the drug for the shortest anticipated allowable residue withdrawal time? Or, should studies be performed such that the animals are exposed to the drug at a point in their production life that is expected to be most common and the bacterial organisms are subsequently studied at the common point in their production life at which they are slaughtered? Or, because some nebulous objectives have been presented in the Framework Document (*i.e.*, effects of withdrawal periods, effects on increases or rates or extents, effects on prolonging durations, etc.), is there intent that the bacteria be studied at multiple time points subsequent to drug exposure (a time course)?

For example, a swine therapeutic to be used primarily in the early growing phase when pigs most commonly have the disease being treated, and the product is anticipated to have a 21-day withdrawal. Which approach should be taken?

<u>Drug Administration Point</u>	<u>Time of Bacterial Evaluation</u>
~6-8 wks of age	At-slaughter (~22 wks of age; 14-16 wks post-exposure); or 21 days post-drug-exposure; or Multiple time points after exposure (but for how long? <i>e.g.</i> , weekly for a max of 6 wks or biweekly until slaughter time, etc.)
21 days pre-slaughter	At-slaughter; or Multiple time points after exposure (but for how long? <i>e.g.</i> , weekly for a max of 3 wks or semi-weekly until slaughter time, etc.)

For tissue residue/withdrawal studies it has always been acceptable to study subjects based upon a common age/weight of their exposure to the drug, regardless that the studied withdrawal slaughter times are the least common, real-world possibilities for the animal (*e.g.*, calves weighing 600 lb may be dosed with the drug, and they may weigh only 650 lb at certain of the slaughter points compared to real-world slaughter weights of >1000 lb). Thus, it would seem acceptable in these pre-approval studies to study younger/lighter-weight animals if such are most economical in terms of cost, time-expenditure and perhaps in terms of piggy-backing with other required studies (*e.g.*, dose titration, clinical efficacy, tissue residue, target animal safety).

It seems prudent to give some definition to “at slaughter.” This could mean animals at the production site ready to exit for slaughter; it could mean animals that have been pre-slaughter stressed (*e.g.*, transported, fasted, etc.) in a simulated manner or in actual lairage; or it could mean literally slaughtered animals. Does it refer to a fecal sample or a carcass sample if “at slaughter?” Also, what is the meaning of “inherent” withdrawal time between treatment and slaughter?

Nature of Resistance Development

The nature of resistance development is one of the stated objectives. Both the terms “rate” and “extent” of resistance development can have multiple meanings; thus clarity in definitions are needed. For example, does CVM envision evaluating speed of resistance selection, proportions, amounts, amounts of change, magnitudes, levels, prevalence, duration, etc.? By what experimental approaches should these be determined? With what degree of statistical power are “rate” and “extent” to be evaluated?

What resistance(s) is to be examined? Should it be just to the antimicrobial that is administered to the animal, or to it and any human drugs to which it is related or may have cross-resistance, or to all or many human drugs that may have a similar spectrum of activity? How will co-resistance selection be dealt with? The definition of resistance (*i.e.*, shift in susceptibility vs. clinical resistance) needs to be clearly stated, especially since pre-approval studies will likely not have the benefit of established NCCLS-type breakpoints.

As a point of reference, in historical 21 CFR 558.15 studies, with growth promoting antimicrobials, the following were the general requirements:

- 10-12 animals in each of two groups (untreated & treated)
- fecal sampling 1X/wk for 6-8 weeks
- testing of 10 different bacterial isolates per animal per sampling
- testing lactose-positive (*i.e.*, primarily *E. coli*) isolates for a drug with G- spectrum, or enterococci isolates for a drug with primarily G+ spectrum
- determining MIC's of each isolate to 10-12 different antimicrobials that represented therapeutics for either or both human and animal health

The Framework Document uses terms of resistance transfer very imprecisely; it is clear that at times the meaning refers to the mode of resistance acquisition (*i.e.*, bacteria to bacteria transferable resistance), yet at other times the terms merely mean the movement of resistant bacteria from animals to humans. It is unclear if there will be requirements for studying bacteria-to-bacteria transferable resistance such as *in vitro* studies to attempt to elucidate mechanisms of resistance acquisition.

Effects of mitigation measures on resistance selection (*i.e.*, rate and extent) are needed. As mentioned below for studies of pathogen load, it is unclear whether this refers to a potential “microbiological withdrawal” period or some other measure relating to food hygiene practices or even on-farm interventions.

Pathogen Load Studies

Historically, information provided by Dr. Diane Fagerberg of C.A.R.E. indicates that through 1992 there have been a total of 21 different feed additive antimicrobials tested in a total of 52 studies (29 salmonella shedding and 23 antibiotic resistance in cattle, swine and poultry). The majority of antimicrobials “passed.” There were, however, a few that “failed,” or were

presumed to have failed, and the data was never submitted to CVM because the project was abandoned by the sponsor. There is no database on antimicrobials that have been administered by other routes, doses, or durations. Prior to requiring pathogen load studies for all product usages, a careful evaluation should be undertaken to ensure that these studies will provide the type of information the CVM anticipates.

The stated assumption in the Framework Document is that the pathogen load in an animal is predictive of the amount of human foodborne illness that is observed. There has been concern that the traditional “558.15” studies do not meet this goal, yet it appears that similar studies are to be developed anyway. Implicit in the requirement for a “pathogen load” study, is the assumption that quantitative viable counts of pathogens, above a baseline norm, will present a greater risk to public health. No evidence exists (that AHI is aware of) that correlates increased on-farm gut concentration or prevalence of foodborne pathogens to increased human disease from those pathogens. Perhaps if one goes to an extreme situation might the correlation become valid, but incrementally elevated counts would be problematic. Thus, while HACCP practices seek to reduce pathogens incrementally at each step of the food processing chain (farm to fork) to fall within a pre-determined tolerable range, there is no established threshold or tolerance for on-farm pathogen “loads.” Furthermore, without some demonstration of the correlation between on-farm data and human disease, it is questionable as to what value the acquisition of such data will have in providing the CVM with information to evaluate a product candidate’s safety.

There are a number of inherent difficulties that can be pointed out if one attempts to acquire such information to establish the relationship. The 1995 NAHMS swine survey provides ample evidence of the multifactorial nature of the issue and highlights the confounding factors that preclude the establishment of a causal relationship.

On-farm surveys showed that fecal salmonella was present in 38% of operations, but regional variation was evident with a range of 30% in the midwest and 65% in the southeast. Larger herds had a higher prevalence of salmonella than smaller herds (57% vs. 32%). Not all pens on all farms tested positive for salmonella; in fact most pens were negative. There was a sex effect with single sex pens twice as likely as mixed sex pens to be positive. Only 6% of the finisher pens were salmonella positive, indicating that salmonella was shed sporadically at low levels. Ten serotypes accounted for 85% of the isolates. Of the serotypes isolated, only 4 were on the CDC’s top ten list of human pathogens but in a non-related order. In other words, *S. agona* was the #2 isolate for swine, but #6 from humans; *S. typhimurium* was #6 from pigs, but #2 from humans; *S. heidelberg* was # 7 in swine, but #3 in man; and *S. enteritidis* BA was #9 from pigs and #1 in man. *From this limited survey, it should be clear that the establishment of a pathogen load relationship will be nearly impossible owing to a host of confounding factors, many of which are not related to antibiotic use.* Not specifically mentioned above is the effect of isolation media on recovery rates, seasonality, vaccinations (against salmonella), etc. but this is discussed in the full text NAHMS document.

Even allowing for “best practice” management on-farm, the final process of slaughter can compromise the microbiological safety of the animals. It is known that transportation stress causes increased shedding of salmonella, even from previously culture negative animals.

Withdrawal of feed can also produce a similar result. Cross-contamination of animals with fecal material can also result in a few “shedders” spreading pathogens to other animals in the pen or cage. No amount of on-farm hygiene, short of raising the animals in a sterile or SPF environment, can eliminate this possibility.

A second objective of the pathogen load studies is to determine the effects of mitigation measures on resistance development. It is not clear as how this is to be done. It seems as though the Framework urges that mitigation studies should be done in tandem with pathogen load studies, in anticipation that the pathogen load studies will “fail.” What mitigation efforts are envisioned; *e.g.*, irradiation of carcasses, extended observation periods post-medication, feed withdrawal or addition prior to transport to slaughter, etc.? Is there the potential that these human microbial safety-related study requirements could dictate animal drug withdrawal times or proscribe certain usage restrictions? What would constitute a universally acceptable, practical and effective mitigation measure? Until such time as additional information on the value and design of conducting mitigation measure studies is available, it is impossible to know what to do to comply with this objective.

For these reasons, the value and relevance of conducting pathogen load studies is questionable. The practicality of obtaining meaningful data from on-farm studies also needs to be assessed.

Sources of confusion relating to Pathogen Load studies

The definition of “pathogen load” is not clearly specified in the Framework Document. Although salmonella, campylobacter, and *E. coli* O157 are listed as pathogens early in the document, Footnote 1 indicates that the definition is basically animal enterics that cause human disease. Other general descriptions of what the study should include are found scattered throughout. For example, in the paragraph prior to Section III, an increase in the bacteria that can cause human infections or prolonging the duration of the carrier state of such bacteria are parenthetically referred to as pathogen load. In Section IV under the heading of Pathogen Load, it refers to pathogen load “at the time of slaughter.” In the paragraph on the “M” exposure category in the section discussing pre-approval studies, the Framework Document refers to pathogen load being reduced prior to slaughter, yet in the paragraph on “H” exposure, it says that the amount of time required for the pathogen load to decrease would need to be determined.

Validation process

Whenever a study design is agreed upon, there must be a CVM sponsored testing period using established products that provides sufficient evidence that all parties can agree provides a validation of the required studies. Since the purpose of the Framework Document is to evaluate new drugs, any information that is generated in this validation study with existing products should not be used for other regulatory purposes. This validation process proposal implies that an expert panel must be established to review the data, and if appropriate, endorse the study design(s) as appropriate for meeting the CVM’s needs.

Summation

Ideally any kind of study would need to be conducted as early as possible in the Development phase (or even late Discovery phase) to determine the potential future regulatory success of the candidate before additional resources are committed. The ability to conduct field studies assumes that there will be adequate clinical trial quality medication, investigators, and budgets available at some stage of development. Because this is a critical success factor, sponsors really must determine prior to this stage whether their candidate will have a likelihood of "passing" or not. This concept must be kept in mind as studies are designed.

A number of technical issues to conducting pathogen load studies have been identified and need clarification and further discussion. Even if these studies are conducted, the Framework Document makes no mention of what criteria will be applied to the experimental results to determine whether the candidate product is "safe?" It is critical that such criteria be known ahead of time.

No mention is made in the Framework Document of providing for a validation period of any new studies to be required of sponsors. Until such time as "paper experiments" can actually be conducted and found to provide the expected data, the fairness and value of requiring such studies is open to question.

Alternative Pre-approval studies

Sponsors are currently required to conduct toxicology and residue studies in the course of their pre-approval studies. The data from these studies are used to set the highest maximum safe dosage for humans and animals, as well as withdrawal times. In combination with these studies, dose determination and clinical dose confirmation studies are conducted to establish "maximum efficacy with minimum drug usage." If the objective of "maximizing efficacy while minimizing resistance" were to be the principle used instead, this could be achieved for some products with a minimum of new pre-approval study revisions. This concept is consistent with the stated goals of the AVMA Judicious Use Principles that the CVM helped to develop. In order to do this, the following proposal is offered.

In the course of drug development, pharmacokinetics and pharmacodynamics are determined for a variety of doses, routes, and durations. The information derived from these early phase studies can be coupled with target pathogen susceptibility data to calculate the most efficacious regimens. A number of papers in the literature speak to this concept which is frequently used to set human antibiotic dosages. An example of such a paper is Pharmacokinetic and pharmacodynamic modeling of antibiotic therapy by P.A. Moise and J.J. Schentag (1999.Curr. Opin. Infect. Dis. 11:673-680). In it, the use of PK/PD parameters such as AUC/MIC and C_{max}/MIC ratios for fluoroquinolones and time above the MIC for beta-lactams, glycopeptides, and macrolides is featured as a rational way to set treatment regimens that

maximize efficacy. While this is beneficial in its own right, the stated need in the Framework Document is to minimize resistance in intestinal bacteria (one could support the notion that this is a mitigation measure by itself). In order to address this aspect, it seems reasonable to obtain sequential fecal samples from animals being used in the PK study and evaluate them for the prevalence, quantity, duration, and susceptibility status of indicator bacteria (a priori chosen to be *E. faecium* and *E. coli*).

A number of limitations will need to be recognized (healthy animals, small number, no foodborne salmonella or campylobacter, no mitigation measures, etc.). Defined study criteria for “pass/fail” will, of course, still need to be developed (balancing efficacy vs. resistant intestinal bacteria selection against agreed standards). This approach offers sponsors the ability to conduct the limited number of studies that they normally do (toxicology, residue, efficacy), but now combining, where possible pharmacokinetic/ pharmacodynamic study data, with the added benefit of addressing resistance selection. If the pre-treatment baseline data on the susceptibility of the indicator bacteria were comparable to the post-treatment data, the resistance development phase would be given a “pass” and pathogen load studies would not be required. If the study did not “pass,” then the sponsor would have the option to pursue the study described next.

Instead of flatly requiring pathogen load studies in animals, an alternative evaluation of carcasses for pathogens, and also testing them for susceptibility to the antimicrobials in question appears reasonable. Animals that were medicated with a new agent could be compared to those in control groups that were treated during efficacy studies done in the field. The “mega Reg” provides baseline prevalence of salmonella contamination rates for carcasses that should be used as the accepted, contemporary standard threshold (other foodborne pathogen tolerances are now being set). It is at this point in the processing chain that a pathogen load effect should be assessed. (A semi-quantitative bacterial count procedure for selected carcasses is also contained in the mega Reg). This allows all of the intervention steps of HACCP to play their role and serves as the best indicator of human exposure, without all of the complications described above for live animals. This step in the chain can also serve as the point source for obtaining isolates for use in the NARMS for serotyping and susceptibility testing. There is even a recent risk model from the USDA ARS using chicken carcasses contaminated with salmonella that offers a much more relevant assessment than the proposed use of animal-derived data (Oscar, T.P. 1998. The development of a risk assessment model for use in the poultry industry. J. FOOD SAFETY.18:371-381). This type of carcass-based testing would provide appropriate information for assessing the amount of resistant foodborne bacteria entering the food chain while avoiding some of the major complications outlined for live animals above.

IV. Thresholds

The Framework Document outlines the concept that Resistance and Monitoring thresholds are required to be established pre-approval to define a level of resistant bacteria in animals that would result in no or insignificant transfer of resistance to human pathogens. In their deliberations, the VMAC Committee stated that they could not provide recommendations on the input requested by the CVM for whether such thresholds could be developed, because the criteria for these thresholds were not available. Indeed, the assumptions in the framework document need further clarification before a sound microbiologically based system can be designed.

More precise definition of resistance terminology is needed. The document makes many references to "increasing resistance," "level of resistant bacteria" and "resistance development". Do these terms mean: (a) lessened susceptibility (*i.e.*, increasing MIC from a baseline or natural population distribution), (b) the classification as susceptible vs. resistant (as defined by the National Committee for Clinical Laboratory Standards), or, (c) microbiological resistance based on the presence of identified genes? The assumption is that the NCCLS criteria or resistance gene(s) will be available during the pre-approval phase, but this may not necessarily be true. The Framework Document implies that the measure of interest will be resistant bacteria in animals, which appears from the Framework Document to be foodborne pathogens in the intestinal tract (see below). Currently there is no process for groups like the NCCLS to establish resistance criteria for animal isolates that become human pathogens, even for established antimicrobial classes, thus making these definitions arbitrary. The Framework Document needs to specify the process through which these definitions will be assigned and reviewed. Also, if the antimicrobial is a new chemical entity, it is unlikely that there will be pre-existing "resistance" determinants in the field, likewise necessitating arbitrary definitions of resistance thresholds. The consequence for not having an appropriate definition of resistance is that the new candidate compound will not be approved.

CVM, in the Framework Document, asks for input on setting resistance thresholds based upon human or animal data, or both. This is a complex issue for a number of reasons, which will need to be addressed. Some food-borne antibiotic resistant bacteria in humans will be attributable to human cross-contamination, foreign travel, and consumption of imported food. Other potential sources of antibiotic resistant bacteria can include soil and water contaminants and companion animals. Resistance levels on-farm may be among the furthest removed situation from the general human population as any animal monitoring can be (*i.e.*, compared to sampling carcasses or the edible products). Given the complexity of sources of resistant bacteria that might cause disease in humans, what will be the procedure for determining the baseline for resistance? Who will determine the baseline? Once established, what will be the procedure for review of the appropriateness of the baseline post-approval? It is essential to have a review done post-approval because the likelihood of establishing a "validated" baseline pre-approval may not be achievable given our current lack of understanding of the complexity of resistance emergence. Finally, will only certain human pathogens or zoonotic pathogens be considered?

It will be necessary to specify which foodborne bacteria will be of interest. Salmonella, Campylobacter, and *E. coli* are mentioned in the Framework Document. The inclusion of enterococci is implied, because it might transfer resistance genes, but owing to the complexity of

animal to human resistance gene transfer and possible subsequent disease causation it should not be included at this time. With the three genera of enteric bacteria listed above, what level of characterization is needed (serotype, phage type, etc.)? Why are animal isolates on-farm preferred over carcass isolates (see Discussion in Pre-approval studies)?

A systematic approach to obtain animal isolates will be needed to set thresholds. What will be the randomization process? What numbers of isolates and what frequency of collection are appropriate? Should the animals from which the bacteria are obtained be healthy or ill, or is it expected that both conditions will be tested? Should the animals have been treated with the candidate antimicrobial or not; if treated, when should the samples be taken? Should the isolates be fecal (if so, when in the animal's life span on the farm?) or from carcasses at slaughter? Should one isolate be considered representative of an entire flock or herd? Should the quantity of resistant bacteria be determined in the sample or is the finding of even one bacterium, through selective enrichment, enough to count as a resistant finding? Is there a geographic requirement? How many geographic sites should be tested? Seasonality? What is the expected duration of isolate collection to establish a trend line for subsequent use? In some cases this has been proposed to be at least 3 years which is too long for a pre-approval study.

If the candidate compound is in a pre-existing antimicrobial class, there will be some baseline resistance (*i.e.*, a bimodal population distribution or a wide range of MICs). This could fluctuate for a variety of reasons not related to usage of the particular agent in question. The potential for co-resistance selection has not been addressed. Other issues concerning baseline resistance are discussed below.

The Framework Document has not described how to use animal isolate data as a gauge or predictor of resistance in bacteria in humans. To begin to correlate these two distantly linked groups, the following data are needed. Using chickens as example, it would be necessary to have relevant bacterial isolates from chickens characterized and tested, then matched to similar human isolates associated with chicken consumption. This would potentially include geographic associations. It would be necessary to know if the human isolate was from a sporadic occurrence or an outbreak (*i.e.*, does a single isolate represent multiple cases?). It would be inappropriate to use "all salmonella" from animals and humans in the comparison. Since there is an implied cause and effect relationship that is being established, it is necessary to minimize as many confounding factors as possible such as non-food sources of the same pathogens.

To conduct the monitoring programs for threshold compliance additional logistic considerations are necessary. Would there be a need for a central laboratory to receive and test all submitted isolates? If each sponsor were to conduct an independent operation, all sorts of complications might ensue such as non-comparable or conflicting data. Additionally, sponsor conducted studies would perhaps be redundant when a single national program could be more efficient and cost-effective. In this way, a central repository for strains would be available to support future discovery needs, multiple antibiotics could be tested head-to-head, and data entry and analysis would be facilitated.

A data analysis package must be developed as part of the overall requirement for the thresholds. Experts in the monitoring "business", such as Dr. Clyde Thornsberry of MRL

Pharmaceutical Services, recommend that at least three years worth of data is necessary to establish a trend, that can be analyzed. Fluctuation in data must be evaluated on the basis of external factors such as animal numbers that affect sample sizes, weather that causes a need for more treatments, epidemic spread of a unique clone, geographic dispersion of animals, humans, and food products, etc. A properly designed statistical analysis must be constructed to account for these normal fluctuations since they affect the sensitivity and specificity of the threshold. The use of modal MICs, MIC₅₀, MIC₉₀, or other interpretations must be discussed in light of the sensitivity of the threshold, either for monitoring MIC shifts or resistance. If the intent is to have the threshold change be so sensitive as to detect subtle MIC shifts (*i.e.*, a few isolates out of hundreds or thousands) then a carefully established correlation process must be developed and proven to be valid. Monitoring can be designed to detect change; however, the question is, what change is relevant, within what time period, and within what geographical region? The inclusion of animal, "HACCP" (*i.e.*, carcass samples), and human isolates must be managed in such a way as to establish a valid correlation. Setting resistance thresholds for animal antibiotic resistant bacteria will be very complex since there is presumption that *any* effects on humans are related to acquisition from contaminated edible products of food-producing animals. Factors contributing to the complexity are (1) time of sampling relative to drug exposure, (2) the organism being monitored (all enterics, G- or G+ enterics, enteric pathogens only), (3) the relative proportion of all marketed animals that received treatment, (4) the likelihood of ultimate contamination load of antibiotic resistant bacteria on edible products, (5) the likelihood that the antibiotic resistant bacteria would be consumed, and (6) the likelihood that any consumed antibiotic resistant bacteria would impact human antibiotic resistant bacterial levels. If the monitoring were more directed, *i.e.*, sampling of carcasses or retail products, the complexity would not be as great, although confounding factors would still need to be addressed. Thus, even this simplification will not be straightforward owing to disparate sample outcomes between various slaughter plants, variation in adherence to HACCP procedures, seasonal variation, plant capacity, and so forth.

The specifics of exceeding a threshold level and causing additional epidemiological investigation or regulatory action must be clearly established before the system is implemented. As mentioned above, the key to making this an effective tool is the establishment of a valid and predictive correlation of animal isolate data to human isolates with similar resistance profiles. For example, if an MIC value is used as the "trigger" for action, should this be determined at one point in time, on a quarterly or yearly rolling average basis, on a continuous basis for a fixed duration, on a given percentage, or an absolute increase without regard to other parameters? Do all of the tested bacterial species need to exceed the threshold or just one? What specific numerical relationship between animal isolates and human isolates is needed to invoke action? How will the threshold account for co-resistance selection among multiply resistant bacteria?

An example scenario for setting a resistance threshold based only upon human data would be:

- Assume baseline human antibiotic resistance is 10%
- Assume it is a category I drug, thus no increase in resistance is tolerable
- Assume no more than 10% of treated animal enterics can be antibiotic resistant.

The implications of this scenario are: (1) if baseline animal enteric antibiotic resistance is already >10%; does that imply the new antimicrobial cannot be developed, and (2) this presumes that any increase in animal enteric antibiotic resistance will have a direct proportionate impact on human antibiotic resistance (*i.e.*, if animal antibiotic resistance was 11%, then human antibiotic resistance would increase by 1% to 11%). Similarly, it would be inappropriate to employ a magnitude of change criterion based only upon human data. For example, a change in human antibiotic resistance from 10 to 10.5% might be considered crossing the resistance threshold, this is equivalent to a 5% change. A similar 5% allowable change in animal antibiotic resistance could be misleading, if animal antibiotic resistance baselines are actually lower, then the example of 5% change could be miniscule; *i.e.*, 5% baseline antibiotic resistance vs. 5.25% post-exposure antibiotic resistant. This scenario is especially applicable for older drug classes (*e.g.*, aminoglycosides, tetracyclines, penicillins, and macrolides) where resistance levels are already high in some bacterial species in both animal and human populations, and the variability with these populations is likewise high.

Resistance and monitoring thresholds can be set based upon animal or carcass data, but also need to be set relative to human data. If resistance thresholds are set for animal or carcass data, and the thresholds are approached, met or exceeded, this will have little relevance if human antibiotic resistant bacteria have not increased from baseline. These developmental aspects should be agreed upon by affected stakeholders and subjected to a validation process to ensure that the exercise is meaningful before it is enacted. Since there are some data already available from the NARMS program, it might be a valuable exercise to use that data as a starting point for discussions.

Threshold Mitigation

Mitigation activities will be resource intensive and must not be enacted without ample justification. Clearly defined and stepwise procedures must be laid out as part of the overall plan. Application of mitigation activities must be taken on the basis of a clearly demonstrated impact on human health, not on the basis of a potential threat. If the latter precautionary philosophy is to be the rule, then all antimicrobial use in animals will be subjected to mitigation events soon after approval. Such a situation is not in anyone's best interests. A key aspect to the effectiveness of mitigation programs is who will be responsible for them. Is it to be the manufacturer(s), a government agency, or other groups, or a combination? The Framework Document specifies that it will be the sponsor who is to instigate the epidemiological studies; however, sponsors are not in the best position to conduct such studies for three main reasons: (1) the lack of expertise, (2) appearance of conflict of interest, and (3) lack of authority to enter farm premises. Careful consideration must be given to this aspect. Again, it would seem that some sort of advisory panel must be established.

The mitigation activities should be stepwise in their intensity and include education on judicious use principles, improved adherence to HACCP processes, and finally, appropriate competitively funded epidemiological studies designed to reduce the appearance of antibiotic resistant foodborne bacteria. Since a trend analysis would require at least three years to establish a baseline, it is reasonable to expect at least a similar period to be applied to monitor the mitigation activities for their effectiveness. As the final stage in such a process, removal of the

antimicrobial is prescribed by the Framework Document. A clearly defined and demonstrated human foodborne bacteria resistance problem of public health significance must be present for which none of the mitigation activities have been effective, there are no alternative therapies available, and there are no additional alternative mitigation actions.

Conclusions and Recommendations

While the concept of thresholds appears to be straightforward, the complexity and implications are tremendous. It will be necessary to empanel a Task Force of experts representing statistical design, epidemiology, microbiological disciplines (food, clinical, diagnostic), drug discovery, medical, veterinary, animal production, risk assessment modeling, and information science to discuss the feasibility of thresholds and the monitoring programs they require. Such a group should include scientific representatives from the USDA (NAHMS, FSIS, ARS), other government agencies, and organizations associated with animal health and production. Meetings and conclusions of this panel need to be ongoing and transparent, with updates on a regular basis because of the complexity and constant change of the issues involved, as well as the lack of an historical base from which to begin. If thresholds are established, their utility in the decision making process also will require periodic review. This proposal is consistent with the VMAC recommendation to establish a sound basis for proceeding. It is likewise consistent with the concept of an advisory board advocated in the 1995 ASM Task Force on Antibiotic Resistance and re-iterated by the 1998 IOM report on antibiotic resistance.

The current NARMS program, with enhancements to be defined by the above Task Force, offers the best opportunity to achieve the data collection goals needed to support threshold action points. The enhancements to be made could potentially include on-farm isolate acquisitions and improved linkage to carcass and human isolates. In this manner, an on-farm aspect could be incorporated into the overall monitoring program, but without making it a separate, duplicative program as inferred in the Framework Document. Consistency of isolate acquisition and MIC generation, at both a pre-and post-approval phase, should facilitate the establishment of a bona fide relationship between animal and human antibiotic resistant foodborne bacteria. Isolates collected through the NARMS program could be made available to sponsors for testing their new antimicrobial candidates at an early discovery phase so as to facilitate the categorization process. Moreover, by generating pre-approval baseline data within the NARMS program, later post-approval monitoring would have a consistent base for comparison.

Any proposed system must be validated, where possible, to ensure that it meets the goals stated in the Framework. The Task Force would need to provide the methods to ensure that the data generated would justify the conclusions made.

V. Post-Approval Studies

AHI supports the VMAC recommendations on post-approval monitoring, *i.e.*, “slaughterhouse data is of paramount importance to the framework. On-farm antimicrobial resistance programs utilizing the farm health quality-assurance programs would be encouraged by the committee to look at post-approval antimicrobial levels for high category antibiotics.” In addition, the VMAC recommendations encouraged the CVM not to make a post-approval on-farm monitoring program mandatory and a condition of approval. The committee went on to endorse the idea that federal, state and local governments should be responsible for the monitoring as it is with other food-borne hazards such as animal drug residues and pesticides, recommending an enhanced National Antimicrobial Resistance Monitoring System (NARMS) program. These recommendations are consistent with the Food Safety from Farm to Table: Report to the President, May 1997. Under this initiative the federal government along with state and local governments, would conduct research, risk assessments and cost benefit analysis along with improving surveillance and investigative efforts to determine how foodborne illnesses occur and can be prevented or controlled in the most efficient and cost effective manner.

It is AHI’s belief that the cost/benefit ratio of monitoring the levels of antimicrobial resistance on farms will be much higher and less definitive than collecting the data from the slaughter houses, which provide for a centralized location for the concentration of animals closer to the consumer. These limited resources would be better spent on increasing the support for the NARMS program.

Not only are the costs of testing prohibitive, concerns have not been addressed as to the confidentiality of the information. Sponsors will have difficulty obtaining the consent of producers to test animals for food-borne pathogens, due to producers’ fears that they may be later implicated as the source of a food-borne illness.

The FDA Framework Document discloses that it would be appropriate to evaluate mitigation measures as well. Presumably, a determination that decreased susceptibility has been found, in either human pathogens or “surrogate animal organisms” (and without regard to whether any change in target animal efficacy has been observed), may be the basis for the initiation of a progressive series of regulatory actions up to and including withdrawal of the product. AHI is interested in determining mitigation measures that could be used to decrease the rate and extent of resistance development in food-borne pathogens, while prolonging the effectiveness of all antimicrobials. It is not scientifically sound, however, to just assume a susceptibility shift detected in slaughterhouse sampling has a direct human health impact.

FDA acknowledges in the Framework Document that the effects of antimicrobial resistance transfer from animals to humans are determined by a complex chain of events which includes the ability of the drug to induce resistance in bacteria; the likelihood that use in food-producing animals will promote such resistance; the likelihood that any resistant bacteria in or on the animal will then be transferred to humans; and the likelihood that such transfer will result in loss of availability of human antimicrobial therapies. Many factors can and do influence the final process of slaughter, which can compromise the microbiological safety of the animal. Transportation stress causes increased shedding of salmonella, even from previously cultured

VI. Summary Conclusions and Recommendations

We share the concern for the potential development of antimicrobial resistance from the use of antimicrobial drugs in food animals. We appreciate the consideration FDA has given to this matter in the proposed framework document but we do have concerns for the impact these changes are likely to have. We also have concern for the scientific evidence cited to justify these changes, as pointed out earlier. In this regard we believe the agency is too ready to accept the conclusion, based on only selected published studies, that food animal use present a significant health risk, the type of data the agency will not accept to demonstrate "substantial evidence" when submitted by sponsors to new animal drug applications. We refer to the proposed rule on substantial evidence which appeared in the November 5, 1997 issue of the Federal Register which is critical of the use of published literature stating, "Published literature, even in peer-reviewed journals, may not be free from error, omission, misinterpretations, or even outright fraud". Yet it seems the agency is willing to rely on such reports to the exclusion of a number of expert reviews which, having considered a much more extensive body of literature, concluded to the opposite; that the evidence is lacking to document a significant health risk.

We would also note that the VMAC also questioned the seriousness of the impact of antimicrobials in food animals on public health and the scientific basis for initiating drastic changes to the approval process. Therefore, we still believe it is necessary to determine the risk to public health prior to deciding on a new framework for regulating animal antimicrobials.

Nevertheless, AHI believes there is common ground on which we can move forward. We accept that the concept of categorization has merit. However, because of difficulties encountered with making distinctions between Category I and II drugs and the fact that circumstances that create those distinctions are likely to change and continue in a state of flux, we suggest a simplified system of two categories: those that are important to human medicine and those that are not important. Appropriate parameters and criteria must be developed with stakeholder input, to make the categorization meaningful.

Furthermore, because an estimate of the presumed exposure of animals to antibiotics does not correlate well with potential increased human exposure, the classification of high, medium and low exposure should be dropped.

We also agree with the framework and VMAC on the importance of post-approval monitoring. We agree with the VMAC recommendations that slaughterhouse data is of paramount importance and that post-approval on-farm monitoring by the sponsor should not be a condition of approval. We support the continued funding and encourage additional support to enhance the current NARMS program so that it can fulfill all the requirements for post-approval data.

The concept of pre-approval studies and establishing monitoring and resistance thresholds is obviously very complex. Much discussion and study is still required to determine the feasibility of a system that can provide meaningful information on which to implement these concepts. AHI is not opposed to the agency evaluating and using MIC trends that could trigger specific actions designed to mitigate the development of resistance. However, given the

complexity of susceptibility changes, we have serious concerns for how the agency can establish specific thresholds that are directly correlated with public health impact. We welcome further discussion on this subject. We also are concerned about the time required to adequately study this issue and develop an acceptable policy. We would expect further research will be required that could involve a number of studies, and even then, the outcome may be that meaningful thresholds cannot be established. Although this area is deserving of more study, a shorter-term solution is needed to address the concern.

Given the dynamics of resistance development and the potential impact on public health, we believe that fixed threshold levels would be difficult to establish and would be subject to constant change based on evolving information about resistance, future availability of new antimicrobials, appearance of new pathogens, impact of pathogen control measures and judicious use principals, and many other factors. It therefore seems more appropriate to evaluate these various factors on a regular basis along with the monitoring data that is being generated to determine levels of resistance or susceptibility shifts that should be of concern based on the situation at that time. This would best be accomplished by a panel of experts representing the necessary areas of expertise such as microbiology, epidemiology, biometrics and risk management.

The expert panel should be appointed immediately and make recommendation on how the NARMS program can be enhanced to provide the necessary data to adequately monitor zoonotic pathogens. The panel should review the data on a regular basis as it is generated to determine if disturbing trends are occurring which require further study or action. Based on a sound evaluation of the risk to human health, epidemiological studies and mitigation procedures would be initiated, as the panel deemed appropriate and necessary. The expert panel would work closely with all stakeholders to ensure cooperation in the common goal of protecting the public health.

Implementation of an enhanced NARMS program along with the establishment of a panel of experts to evaluate evolving shifts in susceptibility would provide a sound system for safeguarding public health. At the same time, it would alleviate the burden of attempting to design pre-approval studies and establish thresholds while lacking adequate information to determine if these measures would have the desired impact on public health.

Finally, regardless of how CVM decides to implement the concepts provided in the framework document, the implementation process will be lengthy. We believe the AHI proposal, however, provides the most expedient means for accomplishing the goal of protecting public health. In the meantime, we strongly encourage CVM to adhere to the VMAC recommendation that the implementation process be accomplished without hindering the progress of antimicrobial applications that are currently pending with the agency. The VMAC further recommended that CVM make a specific determination of how they plan to handle current and new applications until the framework implementation is completed. CVM cannot expect industry to invest in developing solutions to the resistance concerns without providing a stable regulatory environment.

AHI also endorses the VMAC's suggestion for transparency of the implementation process through a series of public meetings of panels of diverse experts to assure the final outcome is based on sound scientific principals. AHI looks forward to being an active participant in this process.

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